Bakteriyofaj Tedavisi

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Sunum Planı

- Diyabetik Ayak İnfeksiyonlarına Bakış
- Bakteriyofajların etki mekanizmaları
- Antibiyotikler yeterli mi?
- Bakteriyofajların Klinik kullanımları
- 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 **%17**'sinde ampütasyon gerekiyor

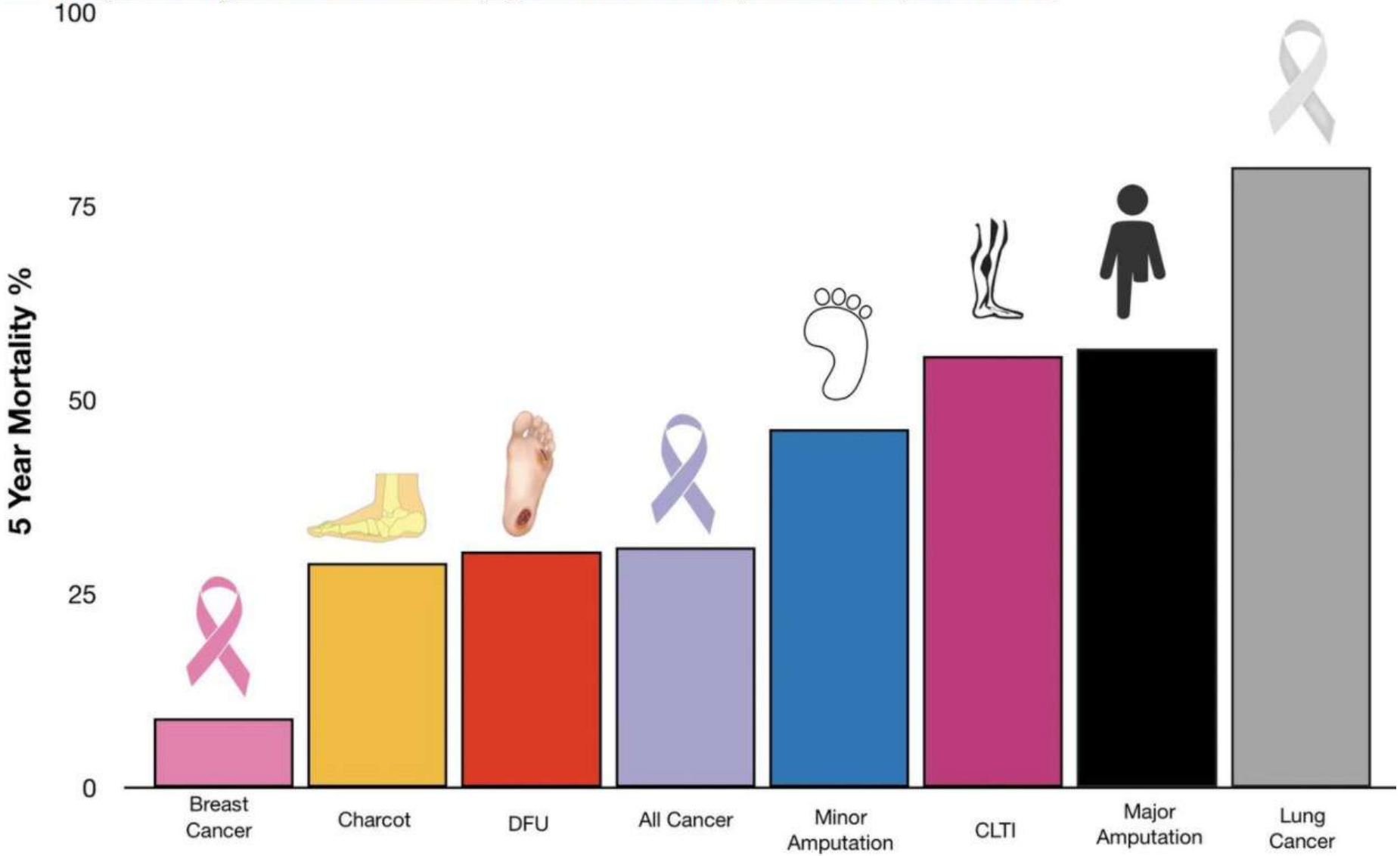
- Amputasyonlu hastalarda mortalite daha yüksek
  - **%49** / 1 yıl
  - **%69** / 5 yıl
  - **%90** / 10 yıl
- Ekonomik yükü:
  - DM 217 Milyar USD / 2017 (ABD) (2012'den sonra %26 artış)
  - DAI 74 Milyar USD /2017 (ABD)
  - Kanser 80 Milyar USD / 2015 (ABD)

DAİ'larında uygulanan AB tedavilerinin başarı oranı %60 oranında..

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]

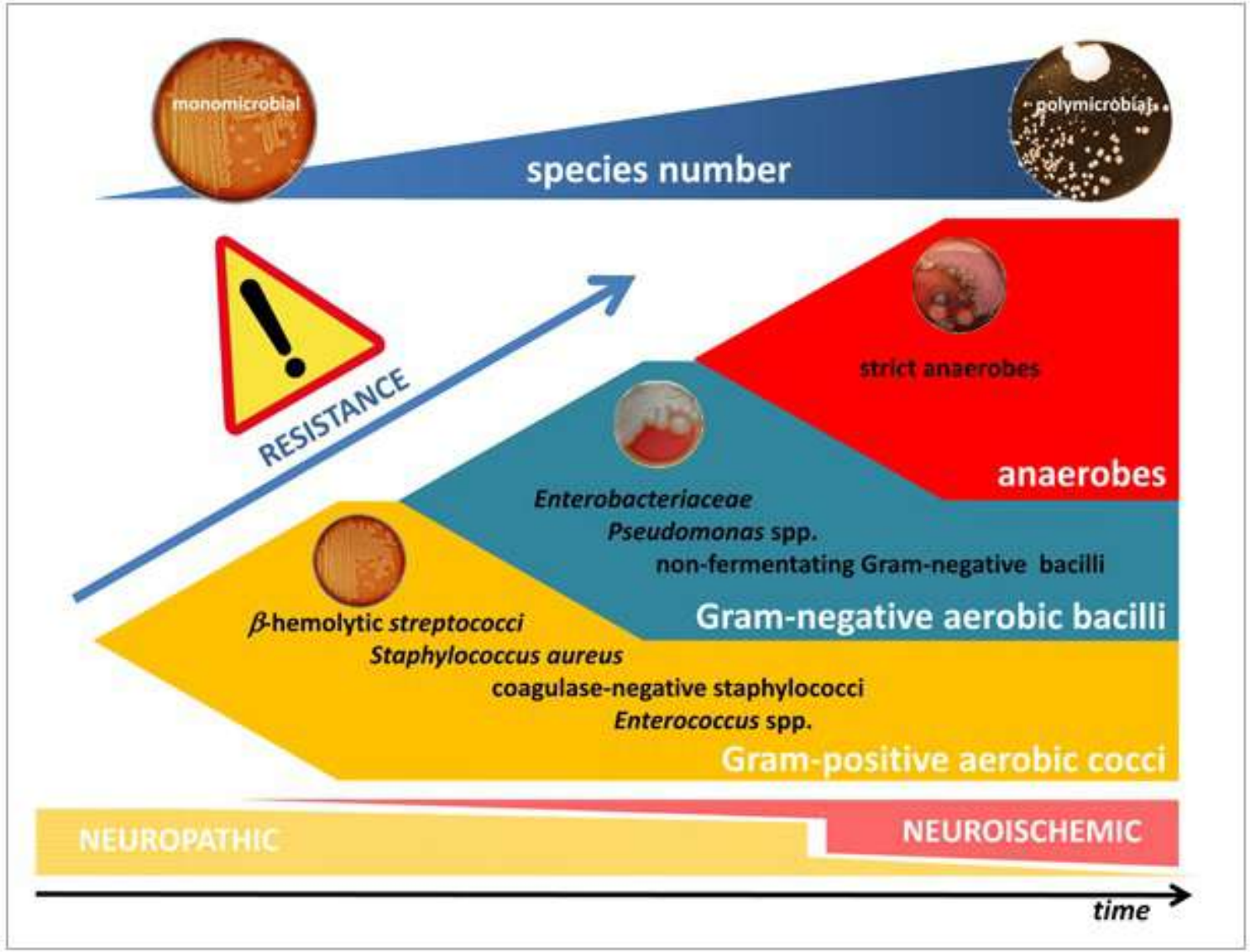
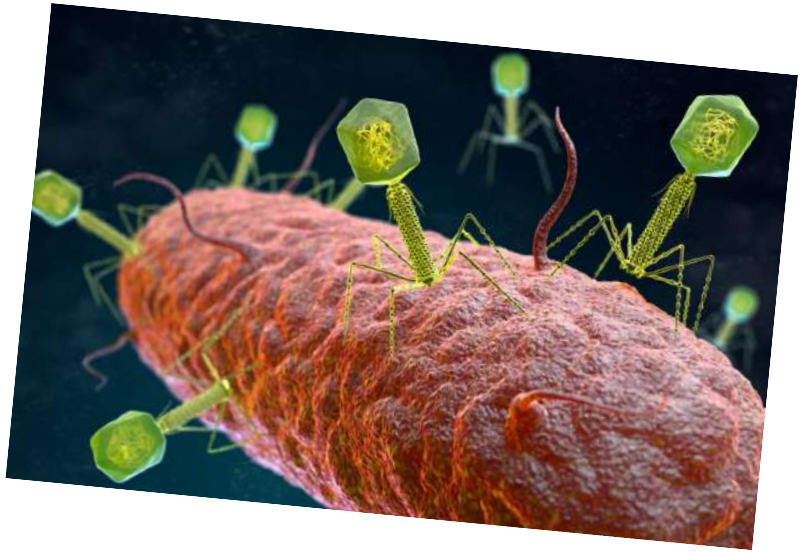


Figure 2: Qualitative and quantitative aspects of diabetic foot infections (DFIs). Staphylococcus aureus and ß-hemolytic streptococci are the first microorganisms to colonize and acutely infect breaks in the skin. Chronic wounds develop a more complex polymicrobial microbiota, including aerobic Gram-negative rods and anaerobes.

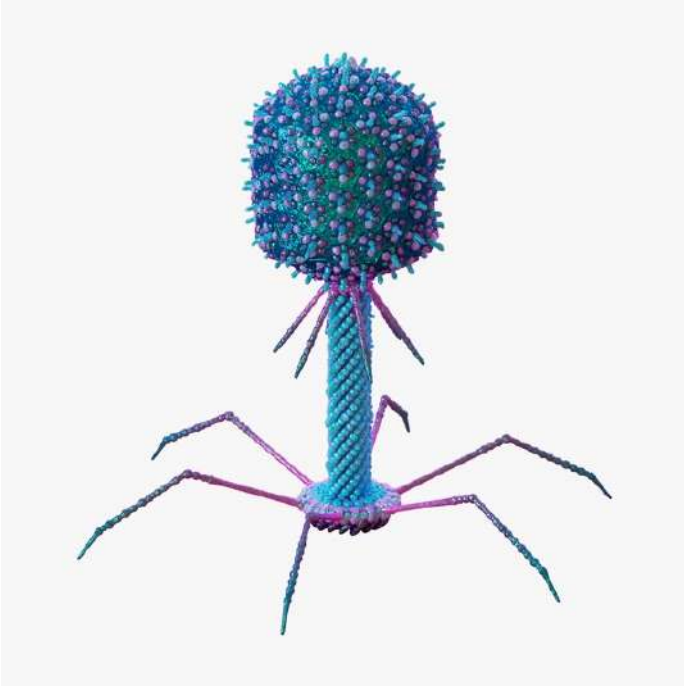
Yeni Arayışlar

- Bakteriyosinler (lantibiyotikler, nisin)
- Esansiyel Yağlar
- Quarum-Sensing inhibitörleri
- Antikorlar
- Nanoteröpatik ajanlar
- Bakteriyofaj Tedavisi

Bakteriyofaj

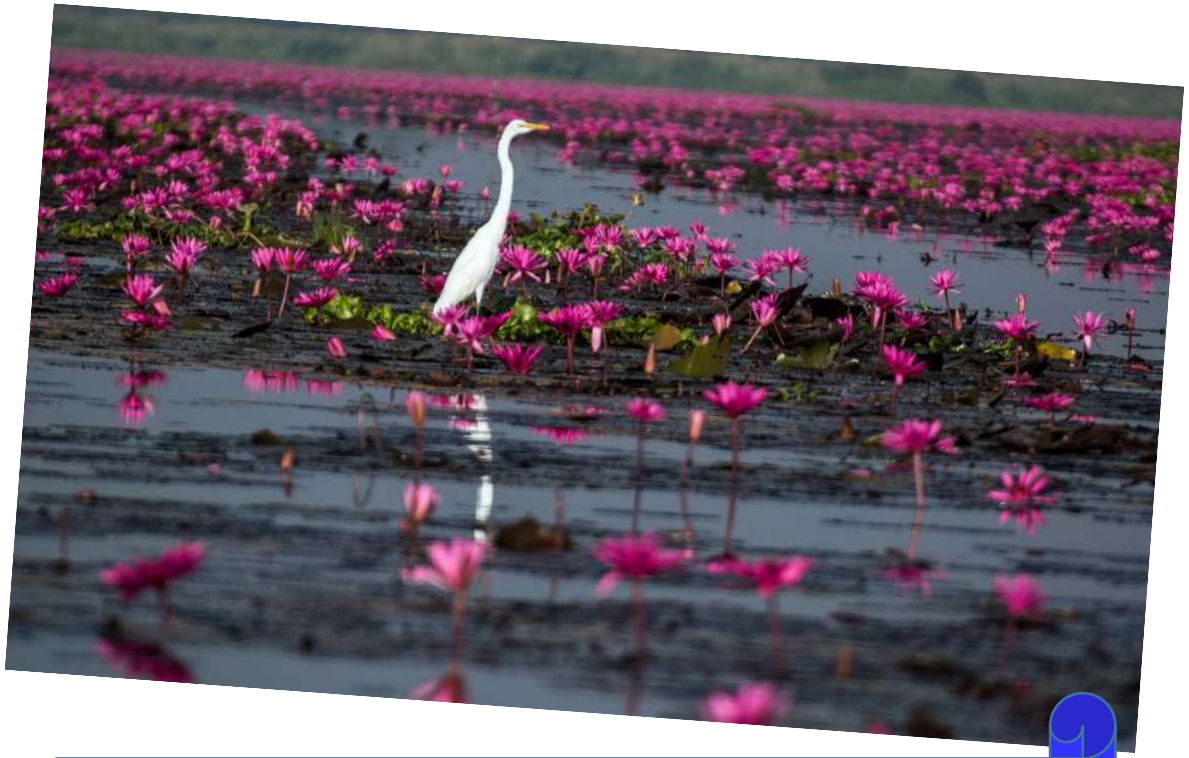


- Bakteriyofaj kısaca faj olarak da bilinir
- Archaea ve bakterileri infekte edebilen virus
- Protein yapısında bir kapsül
- İçerisinde DNA veya RNA genomunu
- Bakterilerin olduğu her ortamda bulunur
- Yeryüzünde 10^{31} 'den daha fazla bakteriyofaj
- GRAS status by FDA in 2006



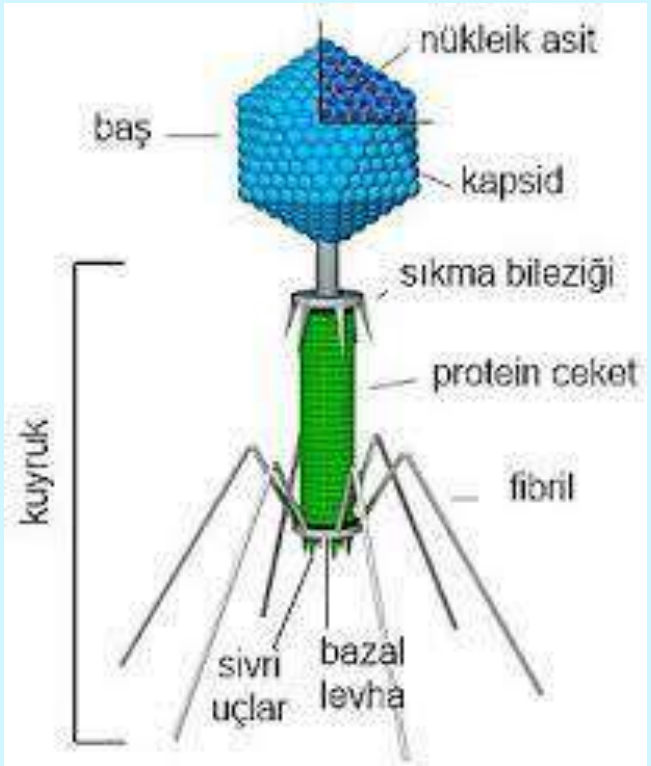
Bulunduğu Yerler

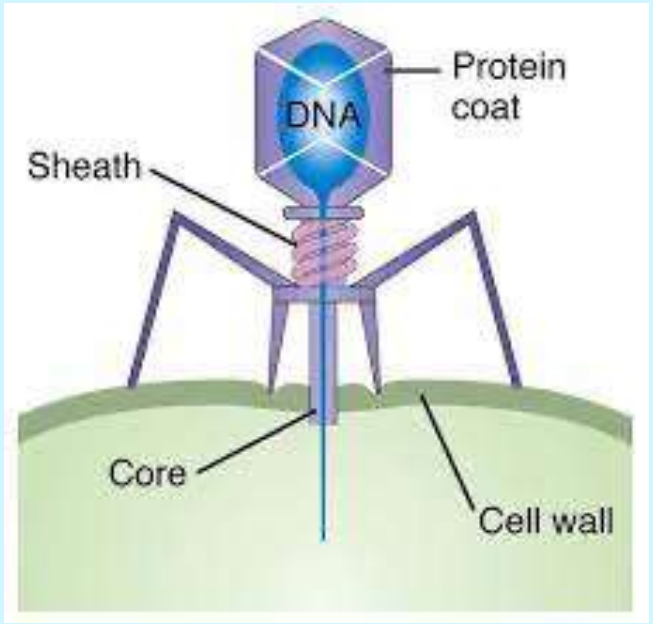
- Deniz suyu bakterilerinin %70'inde
- Tatlı su birikintilerinde
- Kanalizasyon sularında
- Paspaslarda (9×10^8 viryon/mL)
- Yaygın olarak toprakta ve hayvanların sindirim sisteminde bulunur.



Bakteriyofajlar, yakın çevresinde bulunan bakterileri hedef alacak şekilde etkili olurlar.

Bakteriyofaj Yapısı

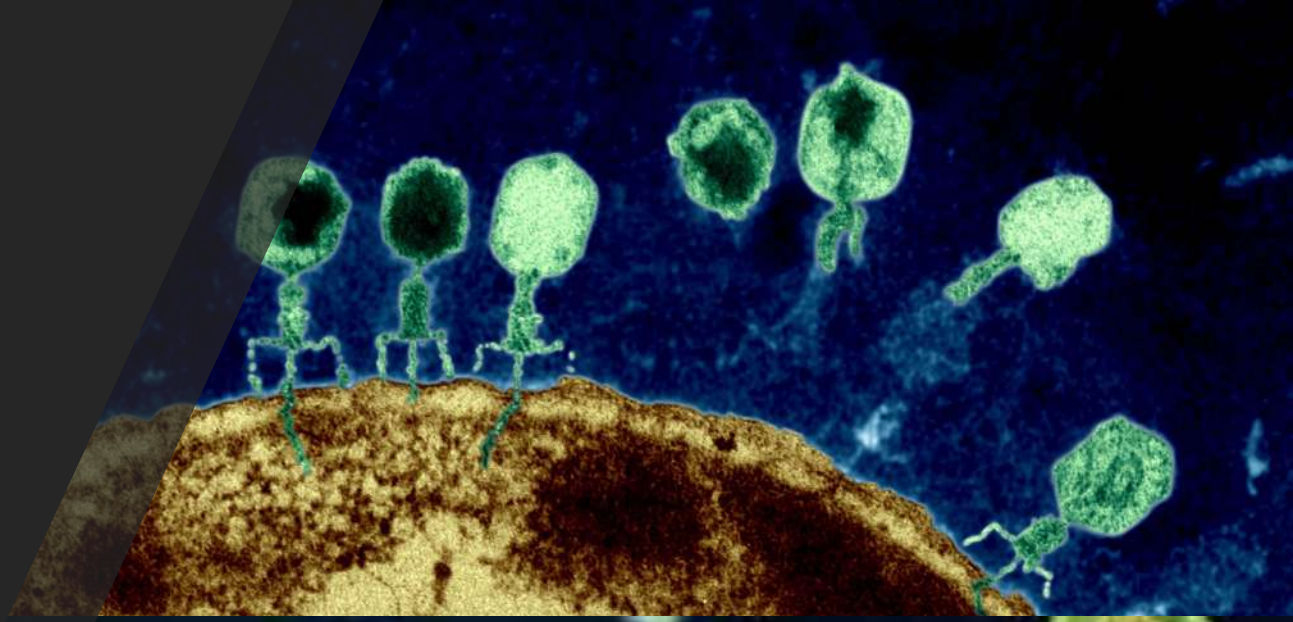


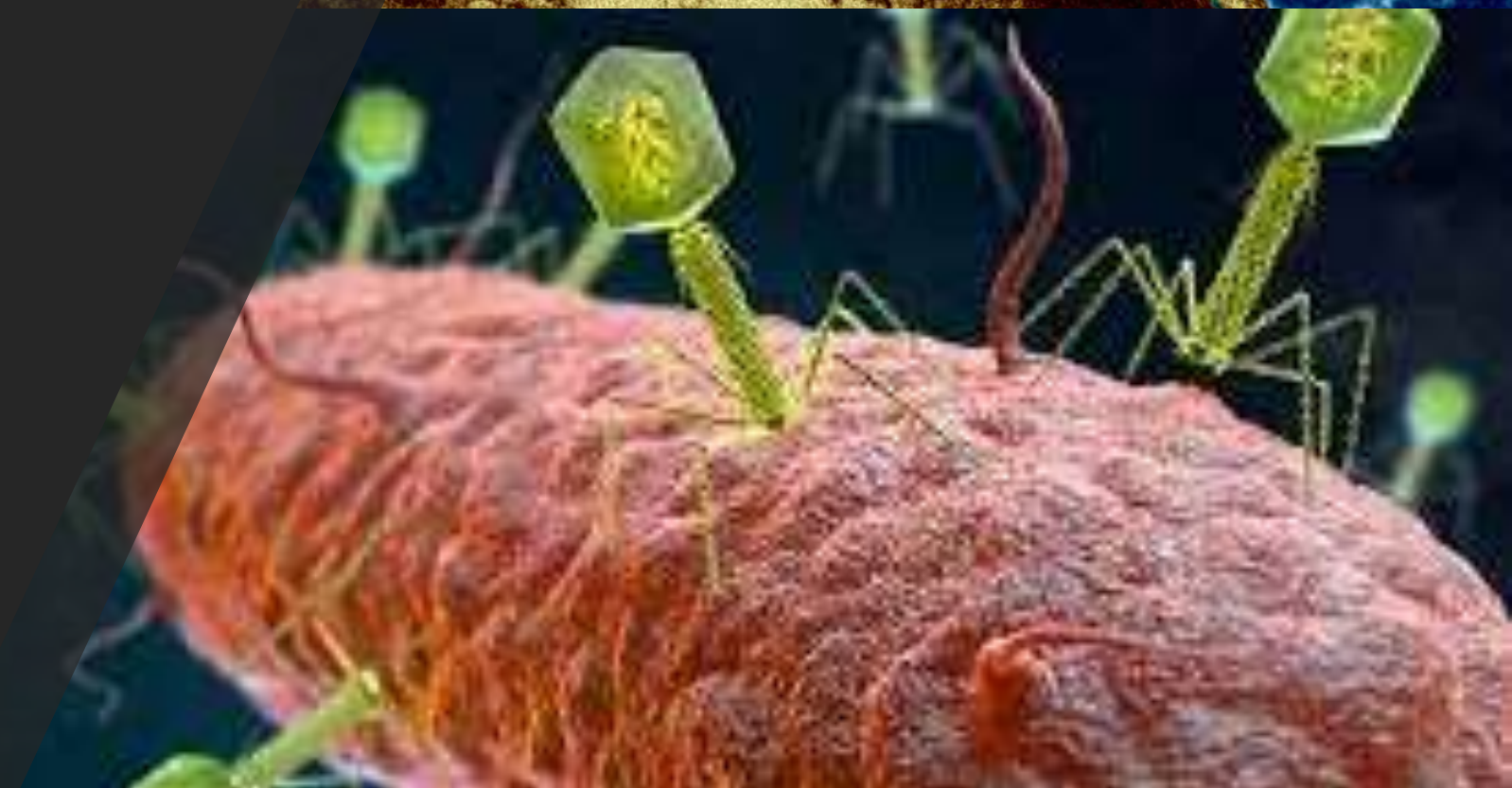


- Baş ve Kuyruk yapısından meydana gelir
- Nükleik asid baş kısmında bulunur
- Fibril uçlarla spesifik reseptörlere tutunur
- Bazal levha ile bakteri hücre zarına oturur
- Bakteri hücre yapısında porlar açılır
- Kuyruk içeriğinden gen aktarımı sağlanır

Tutunma ve Penetrasyon

- Bakteri yüzeyinde spesifik reseptörlere bağlanır:
  - Lipopopolisakkaridler,
  - Teikokik asit,
  - Lipoproteinler,
  - Flagella.



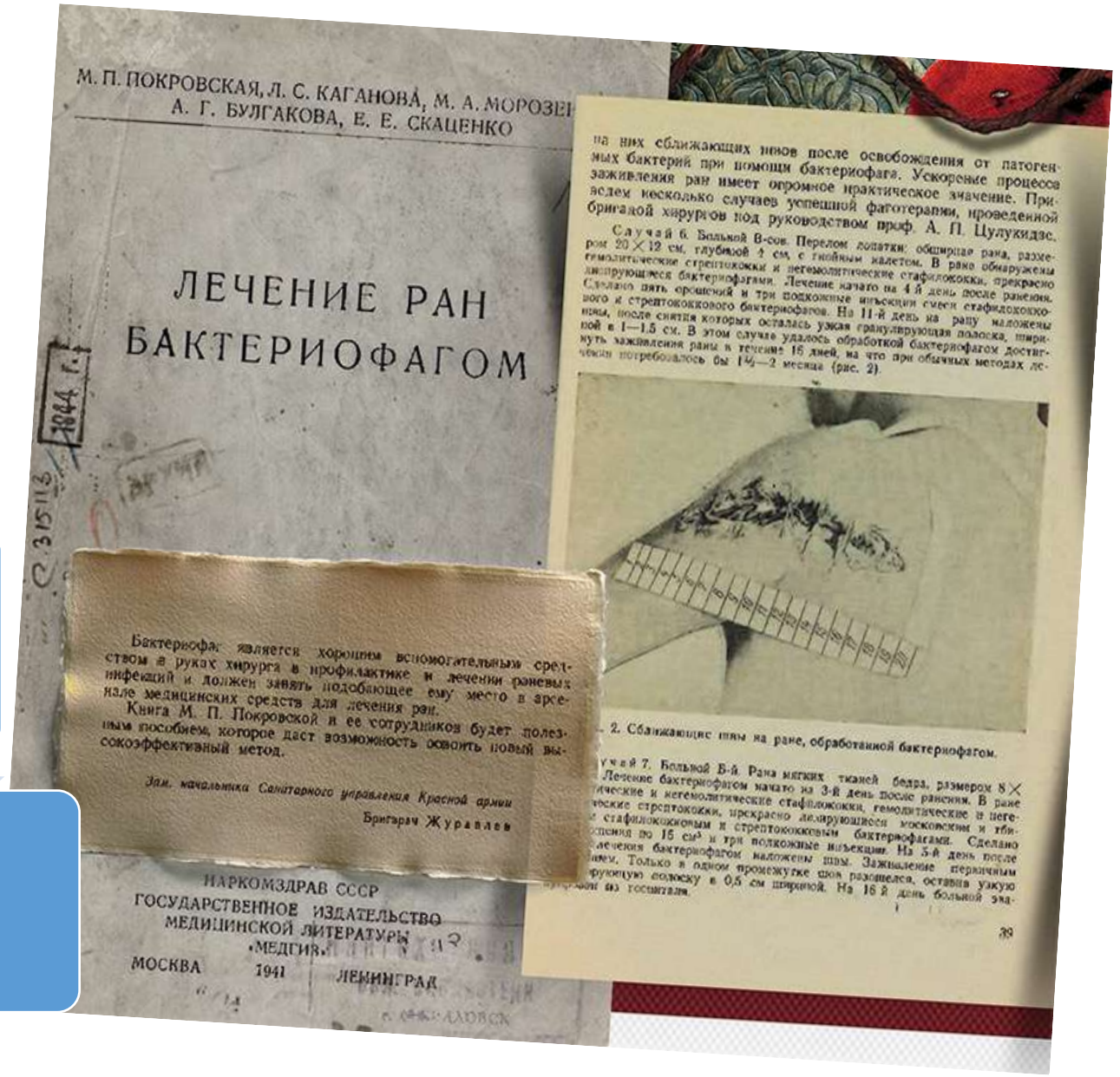


Yaklaşık 100 yıldır antibiyotiklere alternatif olarak kullanılmakta

Eski SCCB (Rusya), Orta Avrupa ve Fransa’da..

Deri ve yumuşak doku infeksiyonlarının tedavisi

Son dönemlerde MDR bakterilerin tedavisinde tercih edilmekte..



Sınıflama

DNA

- 17 Familya
- 8 sirküler
- 9 lineer
- 2 tek zincirli

RNA

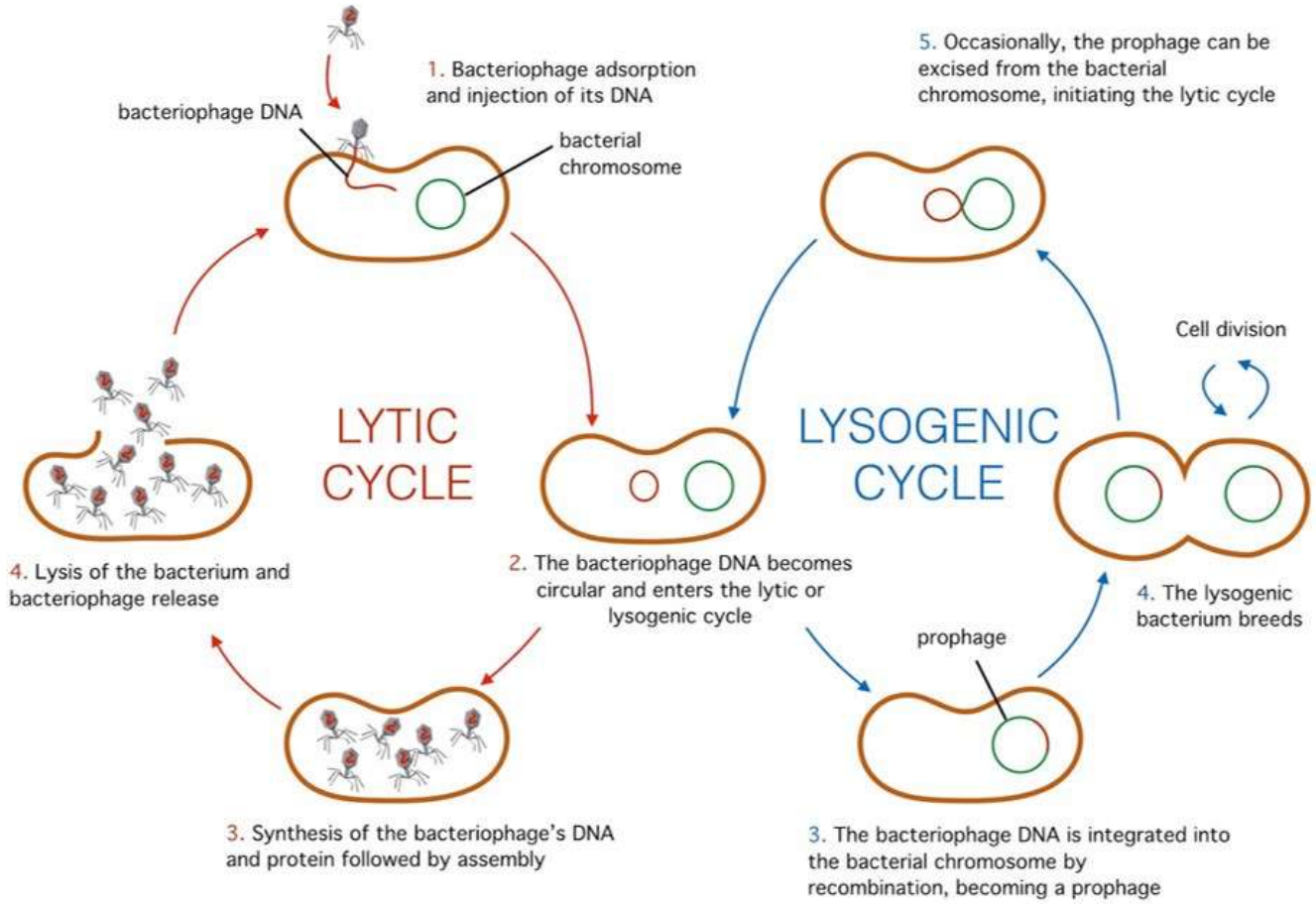
- 2 Familya
- 5 zarflı

Etkinlik

- 9 bakteri
- 9 archaea
- 1 bakteri + archaea

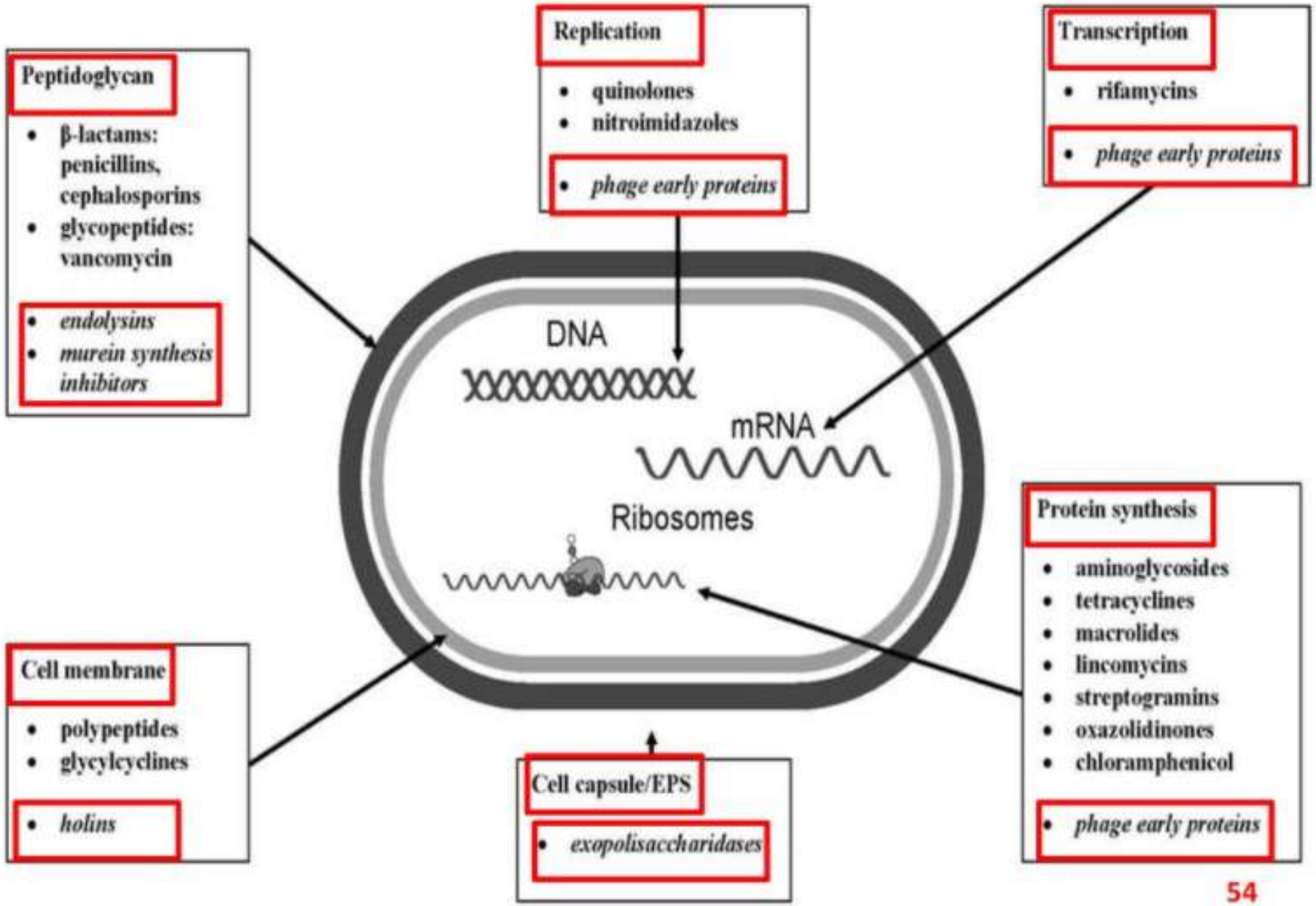
ICTV classification of prokaryotic (bacterial and archaeal) viruses[1]				
Order	Family	Morphology	Nucleic acid	Examples
Caudovirales	*Myoviridae*	Nonenveloped, contractile tail	Linear dsDNA	T4 phage, Mu, PBSX, P1Puna-like, P2, I3, Bcep 1, Bcep 43, Bcep 78
	Siphoviridae	Nonenveloped, noncontractile tail (long)	Linear dsDNA	λ phage, T5 phage, phi, C2, L5, HK97, N15
	Podoviridae	Nonenveloped, noncontractile tail (short)	Linear dsDNA	T7 phage, T3 phage, Φ29, P22, P37

Bakteriyofajların Hayat Döngüsü

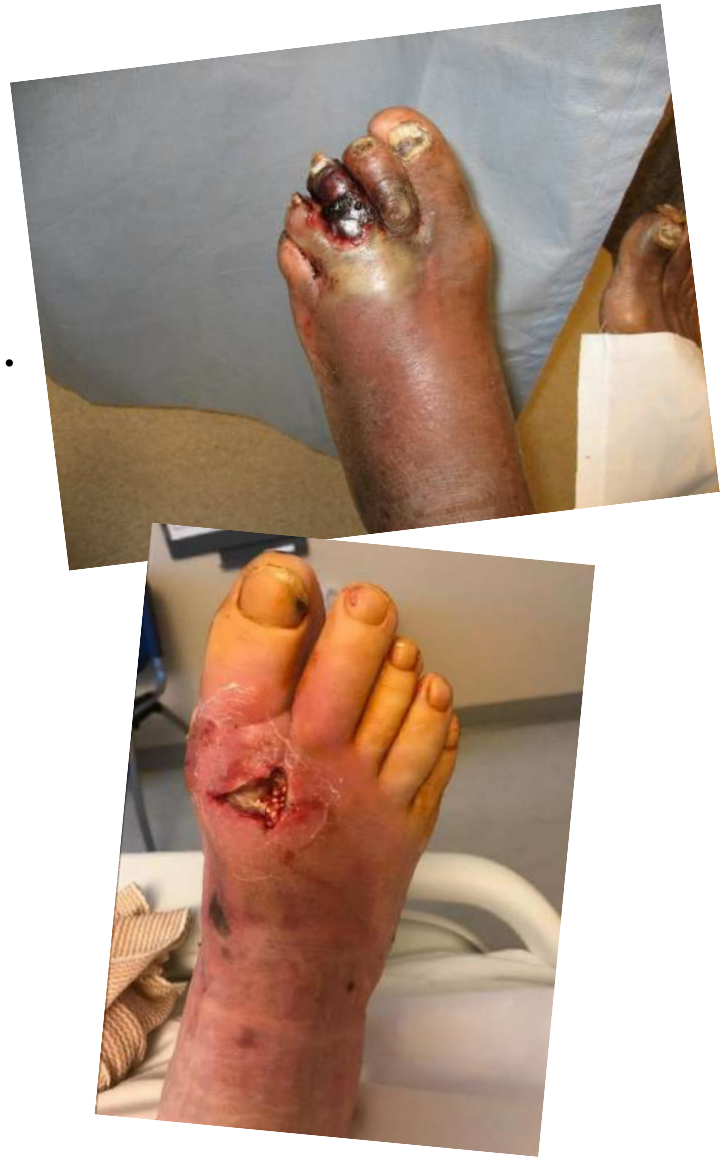


- Bakteriyofajların litik veya lizogenik hayat döngüleri olabilir,
- Lizogenik olabilen fajlara **ılımlı fajlar** (*temperate phage*) denir.
- Konak hücrenin sağlığı yerinde olduğu sürece Virüs sessiz bir şekilde varlığını sürdürür.
- Konağın şartları bozulursa, örneğin besin kaynaklarının tükenmesi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

Sanz-Gaitero, et al, 2014; Callewaert, et al, 2011



- Hastaların immün sistemi düşük, sepsis riski yüksek..
- Üstelik çoğu kez etken Polimikrobiyal.
- Elimizde kültür-antibiyogram olanakları var..
- Ampirik ve rasyonel antibiyotik kullanım politikalarına sahibiz..
- Güçlü kombinasyonlar sağlayabiliyoruz..



O halde Bakteriyofajlara ne gerek var?

Future MICROBIOLOGY

Research Article

In vitro activities of antibiotic combinations against mature biofilms of ventilator-associated pneumonia isolates

Betul Copur*[,1], Sibel Dosler[3], Zerrin Aktas[4], Seniha Basaran[1], Serap Simsek-Yavuz[1], Atahan Cagatay[1], Oral Oncul[1], Halit Ozsut[1] & Haluk Eraksoy[1]

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Background: The authors aimed to determine the efficacy of frequently used antibiotics, alone or in combination, against biofilms of ventilator-associated pneumonia isolates. **Materials & methods:**

In vitro activities of antibiotic combinations against mature biofilms of ventilator-associated pneumonia isolates

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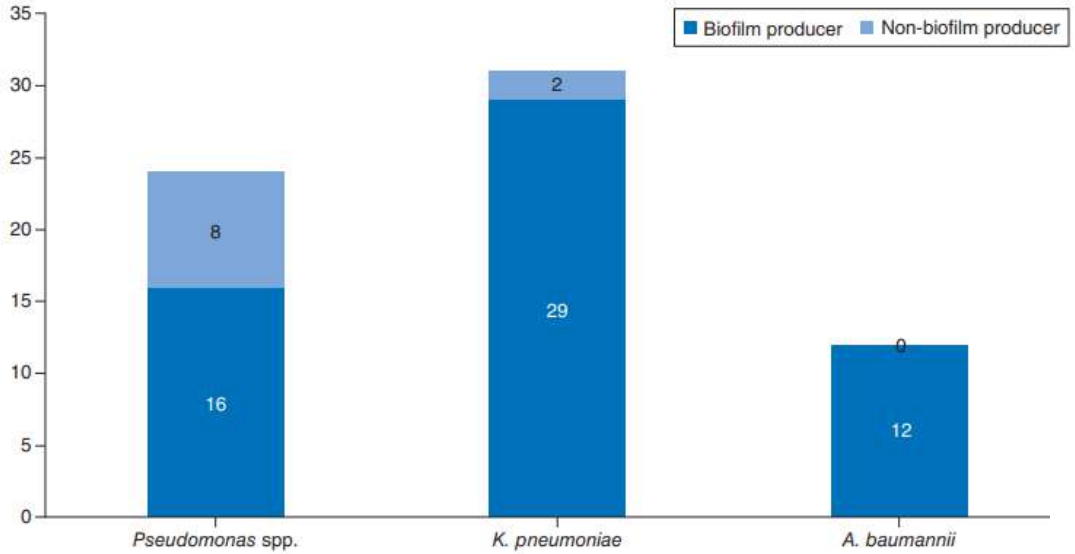
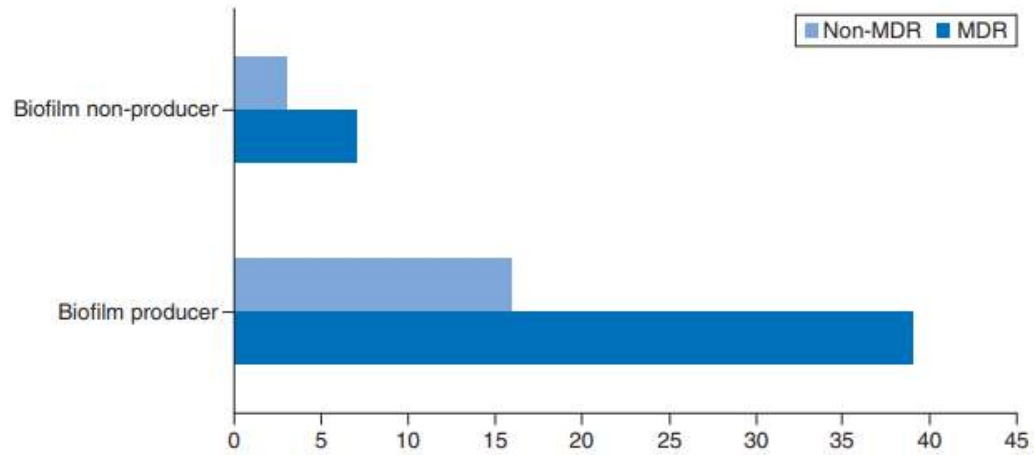


Figure 2. Proportions of biofilm-producing and non-biofilm-producing bacteria.



	MDR n = 46 (%)	Non-MDR n = 19 (%)	p-value
Biofilm producer	39 (71)	16 (29)	1.00
Biofilm non-producer	7 (70)	3 (30)	

Figure 3. Distribution of biofilm-producing bacteria among multidrug-resistant bacteria.

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Table 1. Antimicrobial susceptibilities of 22 *Pseudomonas* spp. isolates.

Antibiotic	MIC values (μg/ml)					Number (%)		p-value
	Breakpoints†		MIC_{50}	MIC_{90}	MIC range	R^- (n = 8)	R^+ (n = 14)	
	S≤	R>						
Meropenem	2	8	8	128	0.12 to 256	8 (100)	6 (42.8)	0.18
Cefepime	8	8	8	32	1 to 64	4 (50)	5 (35.7)	0.66
Amikacin	8	16	16	128	2 to >512	6 (75)	7 (50)	0.20
Piperacillin-tazobactam	16	16	16	128	4 to >512	5 (63)	5 (35.7)	0.18
Ciprofloxacin	0.5	0.5	1	32	0.12 to >512	6 (75)	9 (64.2)	–
Colistin	2	2	1	2	0.25 to 2	0 (0)	0 (0)	1.00

†According to the European Committee on Antimicrobial Susceptibility Testing [18].
MIC_{50}: Lowest concentration of antibiotics producing at least 50% inhibition from *Pseudomonas* spp. isolates; MIC_{90}: Lowest concentration of antibiotics producing at least 90% inhibition from *P. aeruginosa* isolates; R^-: Resistance rates in biofilm-negative isolates; R^+: Resistance rates in biofilm-positive isolates; R: Resistance; S: Sensitive.

Table 3. Antimicrobial susceptibilities of 12 *A. baumannii* isolates.

Antibiotic	MIC values (μg/ml)					Number (%)	
	Breakpoints†		MIC_{50}	MIC_{90}	MIC range	R^- (n = 0)	R^+ (n = 12)
	S≤	R>					
Meropenem	2	8	32	64	0.25 to 64	–	9 (75)
Amikacin	8	16	256	512	2 to >512	–	11 (91.7)
Ciprofloxacin	1	1	64	128	16 to >512	–	12 (100)
Colistin	2	2	0.25	1	0.25 to 8	–	1 (8)

†According to European Committee on Antimicrobial Susceptibility Testing [18].
MIC_{50}: Lowest concentration of antibiotics producing at least 50% inhibition from *A. baumannii* isolates; MIC_{90}: Lowest concentration of antibiotics producing at least 90% inhibition from *A. baumannii* isolates; R^-: Resistance in biofilm-negative isolates; R^+: Resistance in biofilm-positive isolates; R: Resistance; S: Sensitive.

Table 2. Antimicrobial susceptibilities of 31 *K. pneumoniae* isolates.

Antibiotic	MIC values (μg/ml)					Number (%)		p-value
	Breakpoints†		MIC_{50}	MIC_{90}	MIC range	R^- (n = 2)	R^+ (n = 29)	
	S≤	R>						
Meropenem	2	8	4	16	0.25 to 128	0 (0)	10 (34.4)	1.00
Imipenem	2	8	4	16	0.25 to 128	0 (0)	6 (21)	1.00
Ertapenem	0.5	1	16	64	0.25 to 256	2 (100)	22 (76)	1.00
Ceftriaxone	1	2	512	512	0.25 to >512	2 (100)	26 (90)	1.00
Cefepime	1	4	256	512	0.25 to >512	2 (100)	23 (79.3)	1.00
Ceftazidime	1	4	64	512	0.25 to >512	2 (100)	23 (79.3)	1.00
Piperacillin-tazobactam	8	16	512	512	4 to >512	2 (100)	26 (90)	1.00
Amikacin	8	16	16	512	0.25 to >512	1 (50)	13 (45)	0.22
Ciprofloxacin	0.25	0.5	128	256	0.25 to >512	2 (100)	23 (79.3)	1.00
Colistin	2	2	0.25	4	0.25 to 64	0(0)	5 (17.2)	1.00

†European Committee on Antimicrobial Susceptibility Testing [18].
MIC_{50}: Lowest concentration of antibiotics producing at least 50% inhibition from *K. pneumoniae* isolates; MIC_{90}: Lowest concentration of antibiotics producing at least 90% inhibition from *K. pneumoniae* isolates, R^-: Resistance in biofilm-negative isolates, R^+: Resistance in biofilm-positive isolates; R: Resistance; S: Sensitive.

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Table 4. The MIC, minimum biofilm inhibitory concentration and minimum biofilm eradication concentration values of antibiotics against studied *P. aeruginosa*, *A. baumannii* and *K. pneumoniae* isolates.

İsolates	Meropenem			Ciprofloxacin			Colistin		
	MIC	MBIC	MBEC	MIC	MBIC	MBEC	MIC	MBIC	MBEC
P11	16	>4096	>4096	2	256	512	1	>4096	>4096
P18	4	>4096	>4096	4	8	16	2	16	64
A10	16	4096	>4096	128	>4096	>4096	1	>4096	>4096
A13	32	>4096	>4096	128	>4096	>4096	8	>4096	>4096
K7	≤0.25	>4096	>4096	0.5	4096	>4096	1	512	1024
K11	16	>4096	>4096	64	>4096	>4096	8	>4096	>4096

A10, A13: *A. baumannii* isolates; K7, K11: *K. pneumoniae* isolates; MBEC: Minimum biofilm eradication concentration; MBIC: Minimum biofilm inhibitory concentration; P11, P18: *P. aeruginosa* isolates.

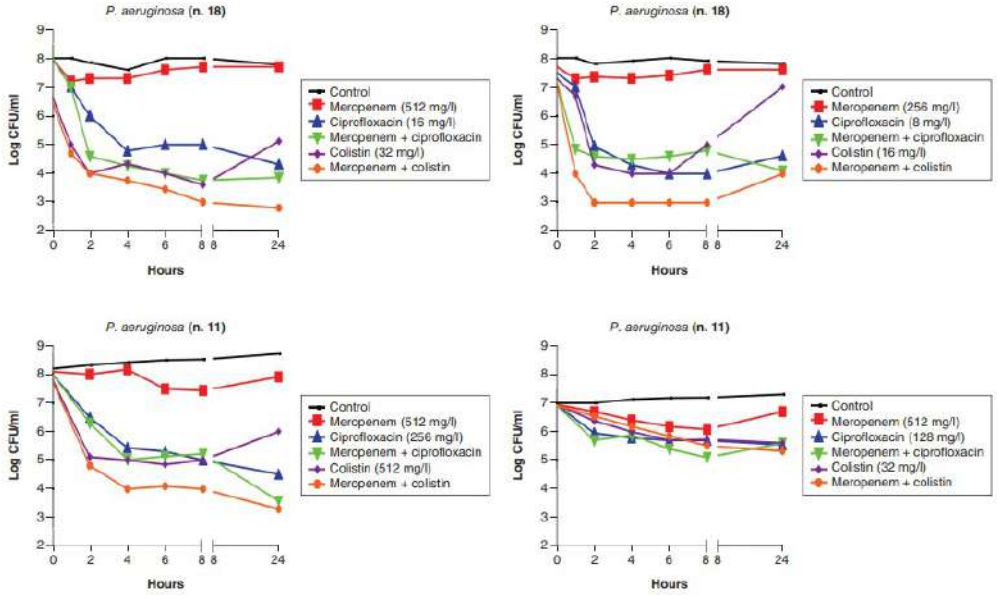

Figure 4. The time–kill curves of the meropenem-colistin and meropenem-ciprofloxacin combinations in different concentrations against *P. aeruginosa* (P18 and P11) isolates. The x-axis represents the killing time, the y-axis the logarithmic *P. aeruginosa* survival.

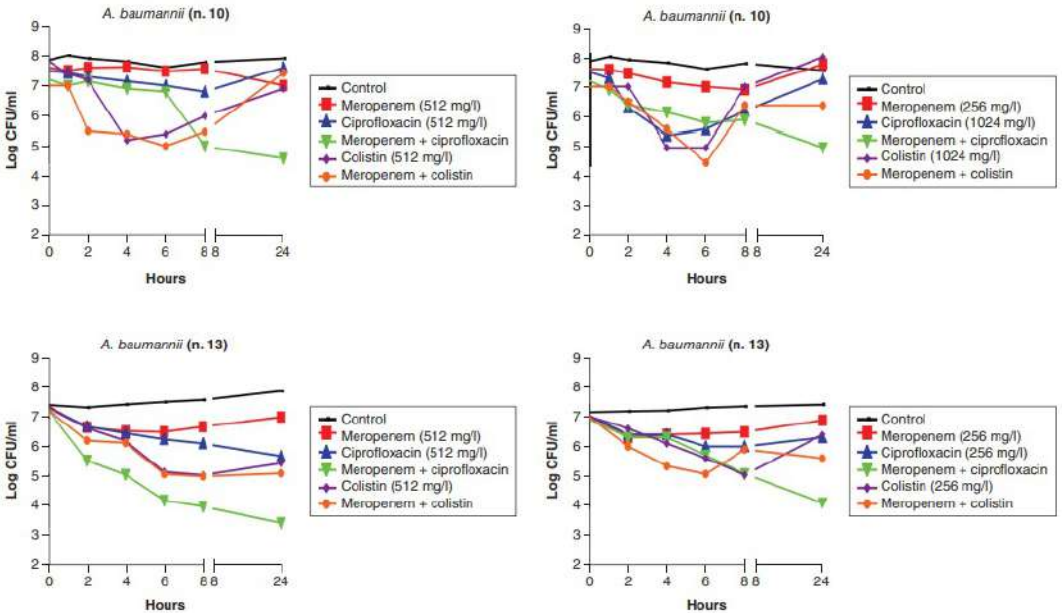

Figure 6. The time–kill curves of the meropenem-colistin and meropenem-ciprofloxacin combinations in different concentrations against *A. baumannii* (A10 and A13) isolates. The x-axis represents the killing time, the y-axis the logarithmic *A. baumannii* survival.

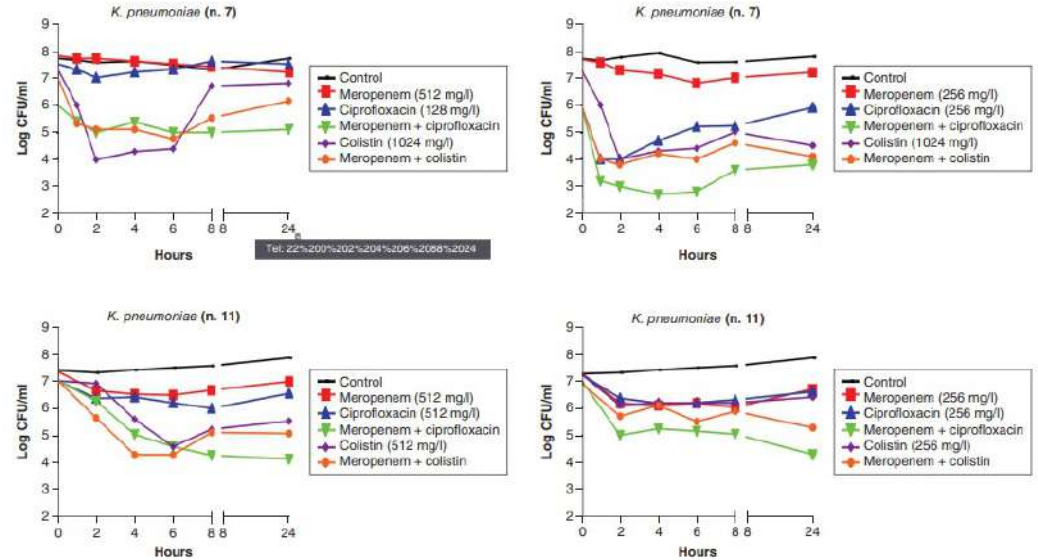

Figure 5. The time–kill curves of meropenem-colistin and meropenem-ciprofloxacin combinations in different concentrations against *K. pneumoniae* (K7 and K11) isolates. The x-axis represents the killing time, the y-axis the logarithmic *K. pneumoniae* survival.

Summary points

- Common causes of ventilator-associated pneumonia, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*, generally have biofilm-forming potential; therefore, the effects of antibiotics could be changed.
- Both the minimum biofilm inhibitory concentration and the minimum biofilm eradication concentration values of meropenem, colistin and ciprofloxacin were found to be 256–1000-fold higher than their MIC values.
- The investigation of the isolates' biofilm-forming capacities and the determination of minimum biofilm inhibitory concentration and minimum biofilm eradication concentration values of antibiotics may be useful approaches for treatment success.
- The biofilm-producing Gram-negative bacteria were not affected by the therapeutically achievable antibiotic concentrations alone.
- There might be a synergistic effect in different concentrations of meropenem-colistin and meropenem-ciprofloxacin combinations against biofilms of *P. aeruginosa, K. pneumonia* and *A. baumannii* isolates.
- Although the combination of meropenem and ciprofloxacin seemed to be a good candidate for the treatment of biofilm-associated infections, the concentrations obtained as a result of the synergy test were above the therapeutic limits.
- The limited treatment options for biofilm infections show the importance of the uninterrupted application of infection control measures and rational antibiotic use.

- Bakteriyofajların biyofilm tabakasına etkinliği var mıdır?
- Varsa nasıl etkili olurlar?

frontiers in Microbiology

REVIEW
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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]**

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[2] *Laboratory of Gene Technology, Katholieke Universiteit Leuven, Leuven, Belgium*

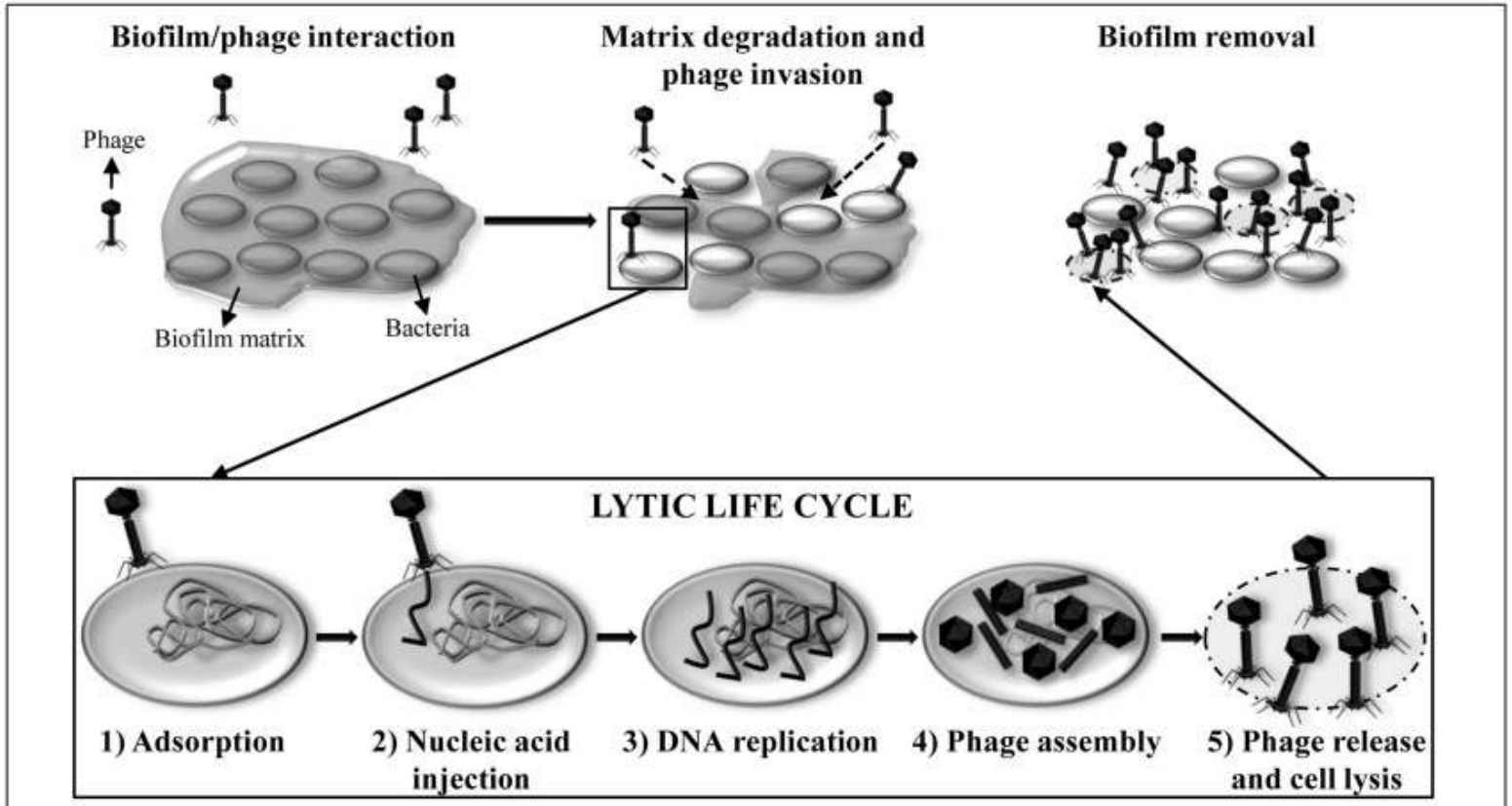

FIGURE 3 | Lytic life cycle of phages inside a biofilm. (1) Adsorption of the phage particle onto the host bacterial cell surface. Tail fibers bind to specific receptors on the cell surface. **(2)** Injection of the nucleic acid into the cytoplasm of the host bacterium. **(3)** Replication of the phage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

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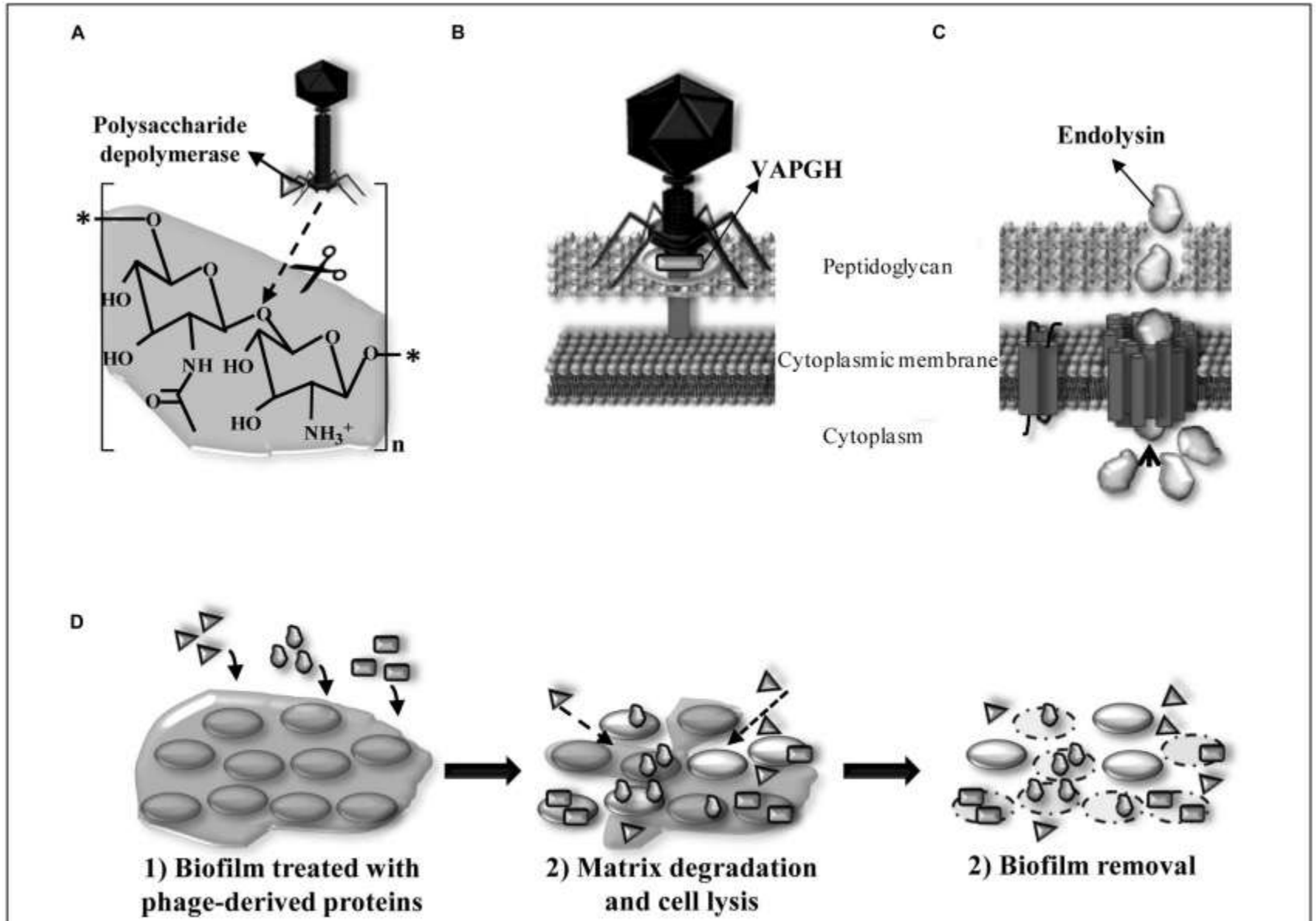

FIGURE 4 | (A) Location of exopolysaccharide depolymerase degrading β-(1,6) bonds of the biofilm extracellular matrix (PIA/PNAG) of staphylococcal species in the phage particle and mode of action. **(B)** Location of virion-associated peptidoglycan hydrolase (VAPGH) at the phage particle and its role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

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RESEARCH ARTICLE
Therapeutics and Prevention

Phages versus Antibiotics To Treat Infected Diabetic Wounds in a Mouse Model: a Microbiological and Microbiotic Evaluation

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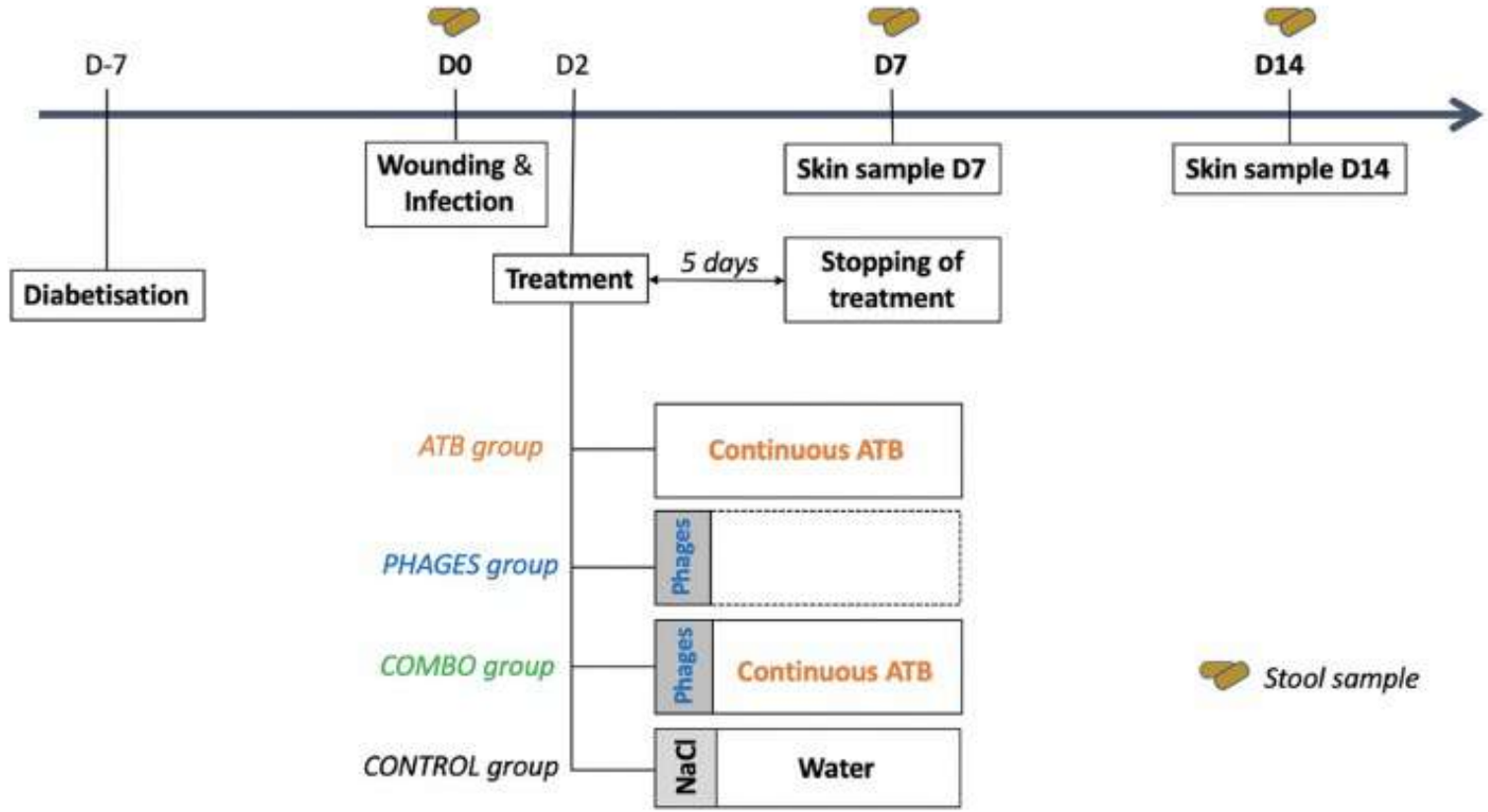

FIG 1 Diagram of the therapeutic strategy. Amoxicillin-clavulanic was administered at a dosage of 60 mg/day *per os* for 5 days, and phages were administered through a unique local administration. ATB, amoxicillin plus clavulanic acid; combo, combination of antibiotics and bacteriophages.

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TABLE 1 Bacterial loads at day 7 and day 14 of infection in skin samples

Group[a]	CFU/g tissue			CFU/g tissue		
	Day 7	Difference from control	*P* value	Day 14	Difference from control	*P* value
Control ($n = 33$)	9.40 ± 0.69			8.20 ± 1.50		
ATB ($n = 24$)	8.54 ± 0.88	−0.86	0.002	7.70 ± 1.19	−0.5	0.2
Phages ($n = 25$)	6.92 ± 0.50	−2.48	3.85×10^{-8}	5.42 ± 2.03	−2.28	7.8×10^{-4}
Combo ($n = 24$)	7.34 ± 0.87	−2.06	1.26×10^{-6}	6.42 ± 1.75	−1.28	0.02

[a]*n*, number of animals in each group.

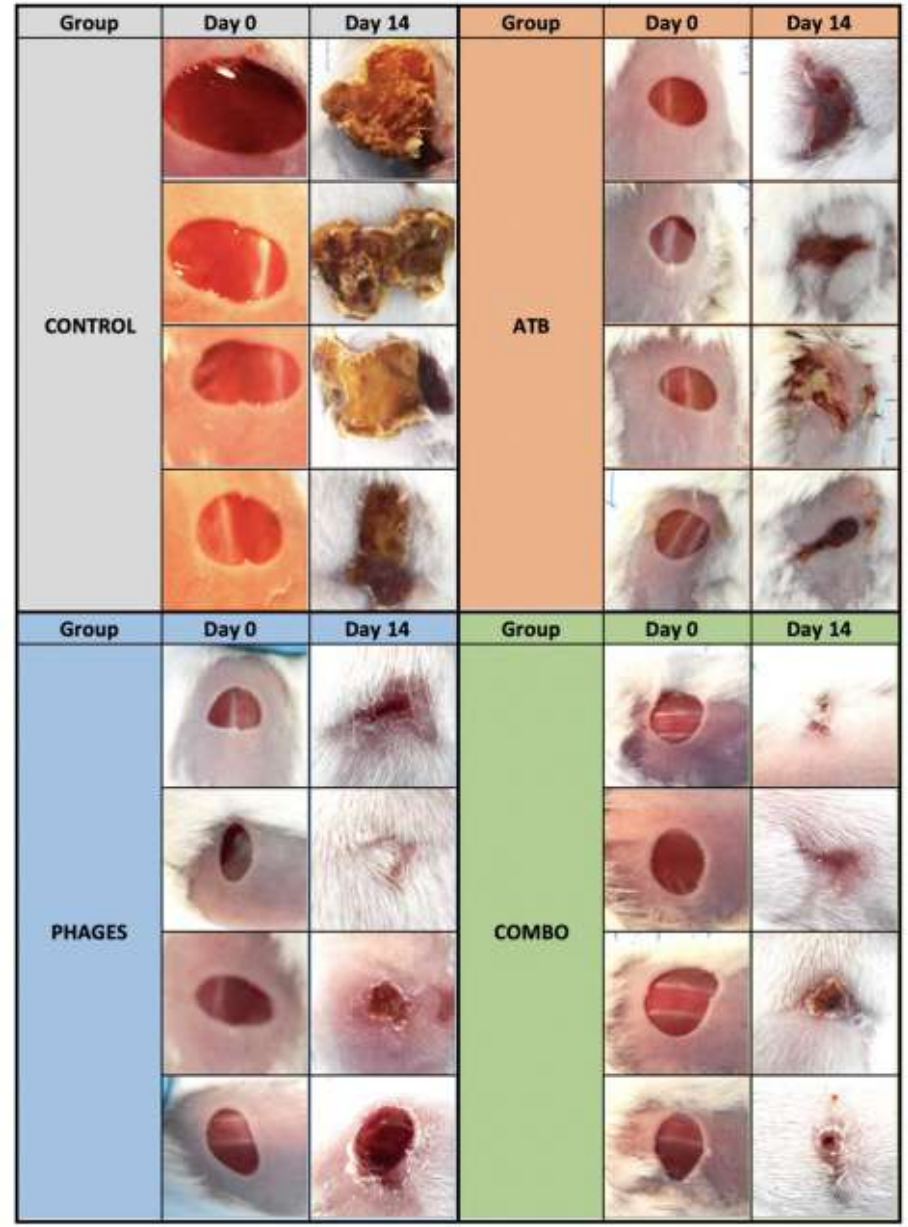

FIG 3 Evolution of wounds in each group (control or treated with ATB, phages, or combo) at days 0 and 14. In each group, each line of photos illustrates the evolution on the same animal.

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Antibiyotik ya da Antibiyotik + Faj tedavisi mikrobiyotada önemli değişime neden oluyor..

Phage Therapy for the Treatment of Infected Wounds

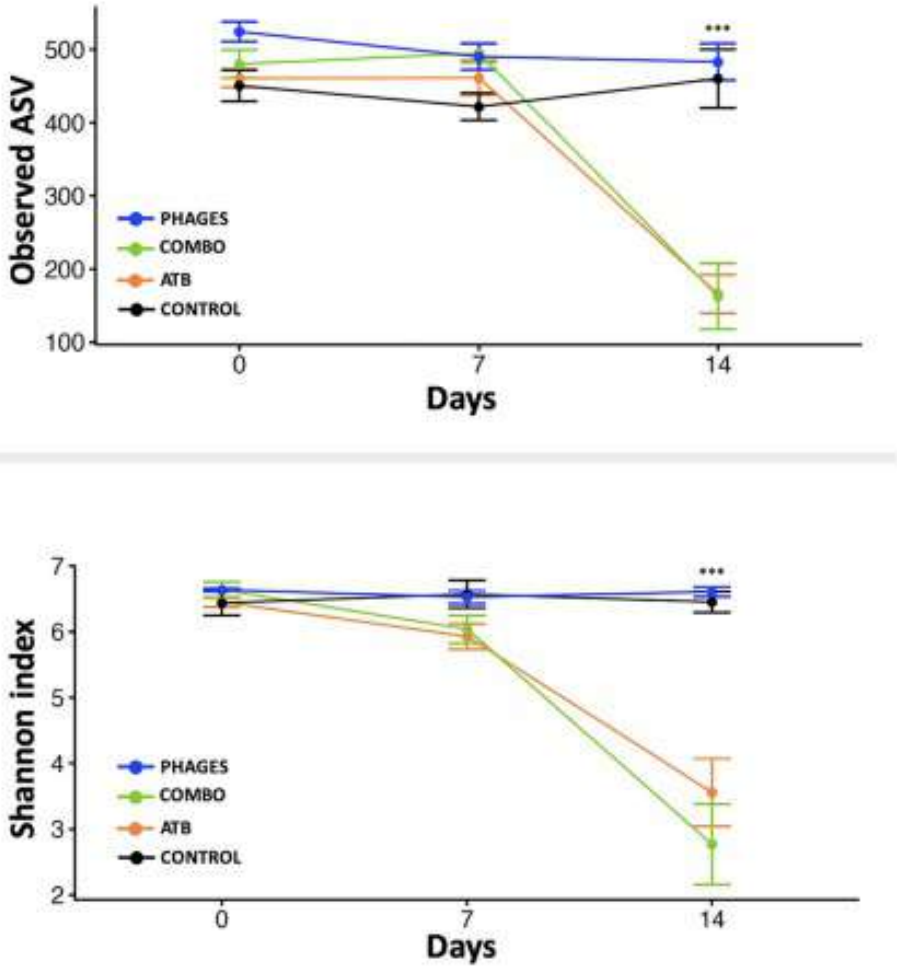

FIG 4 Alpha diversity indices in samples collected from ATB-, combo-, or phage-treated mice and control mice. Analyses were performed on 16S rRNA gene V4 region data.

Phages versus Antibiotics To Treat Infected Diabetic Wounds in a Mouse Model: a Microbiological and Microbiotic Evaluation

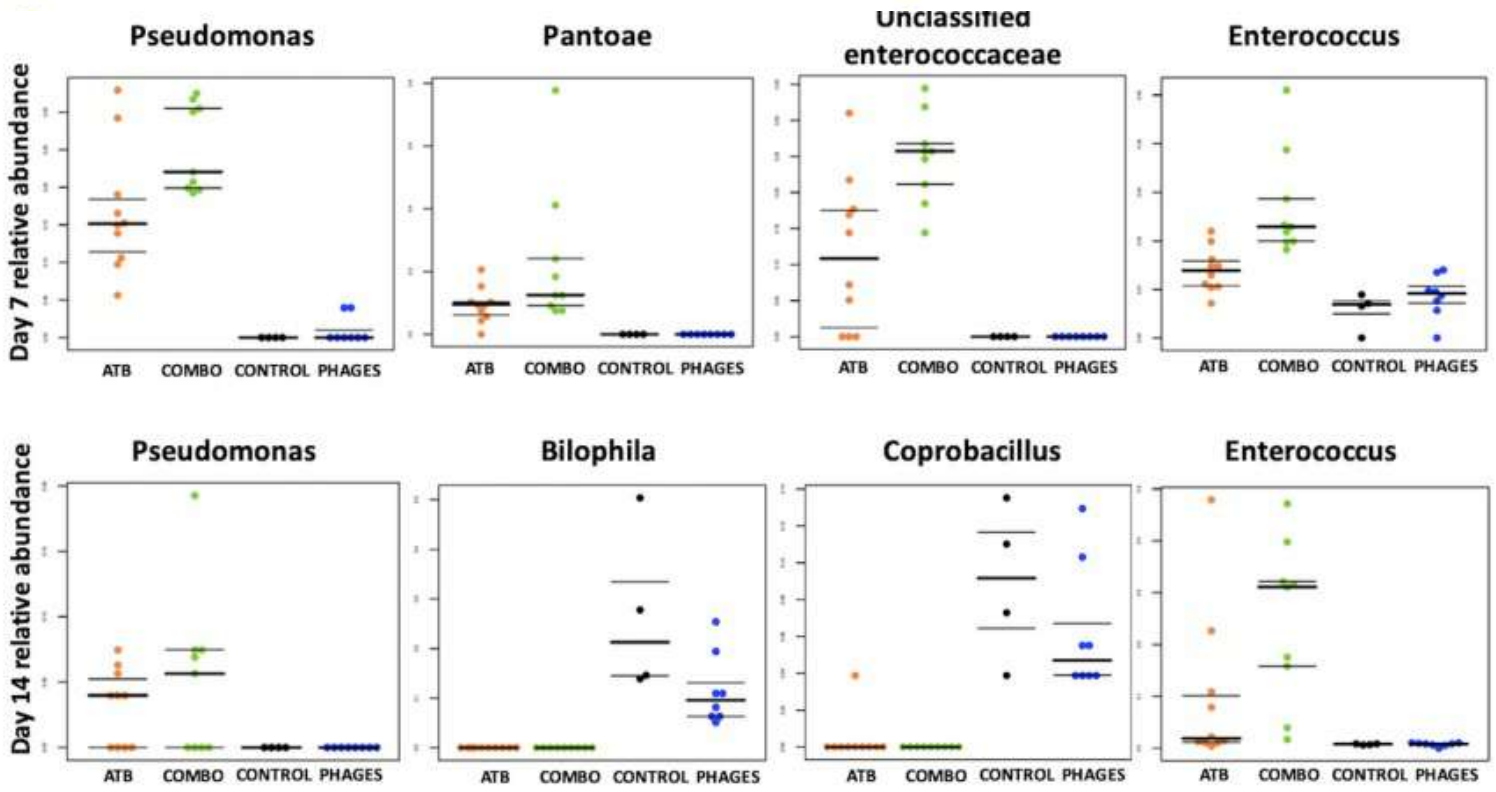

FIG 8 Relative abundances of the most significant genera that were significantly different between the 4 groups of mice at day 7 and day 14 using ANOVA.

ATB or combo treatment compared to that in control and phage-treated mice (ANOVA, FDR-corrected P value < 0.05). At the genus level, the relative abundances of two genera were significantly different between the 4 groups at day 0; 59 genera among 229 (26%) were significantly different at day 7 (including *Pseudomonas*, *Pantoea*, and *Enterococcus*, which were increased in ATB or combo mice) (Fig. 8), and 36 (16%) were significantly different at day 14 (including *Pseudomonas* and *Enterococcus*, which were increased in mice treated with antibiotic or antibiotic plus phages) (Fig. 8). Moreover,

Patojen bakteriler üzerine yüksek selektif etki

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The Threat of Antimicrobial Resistance on the Human Microbiome

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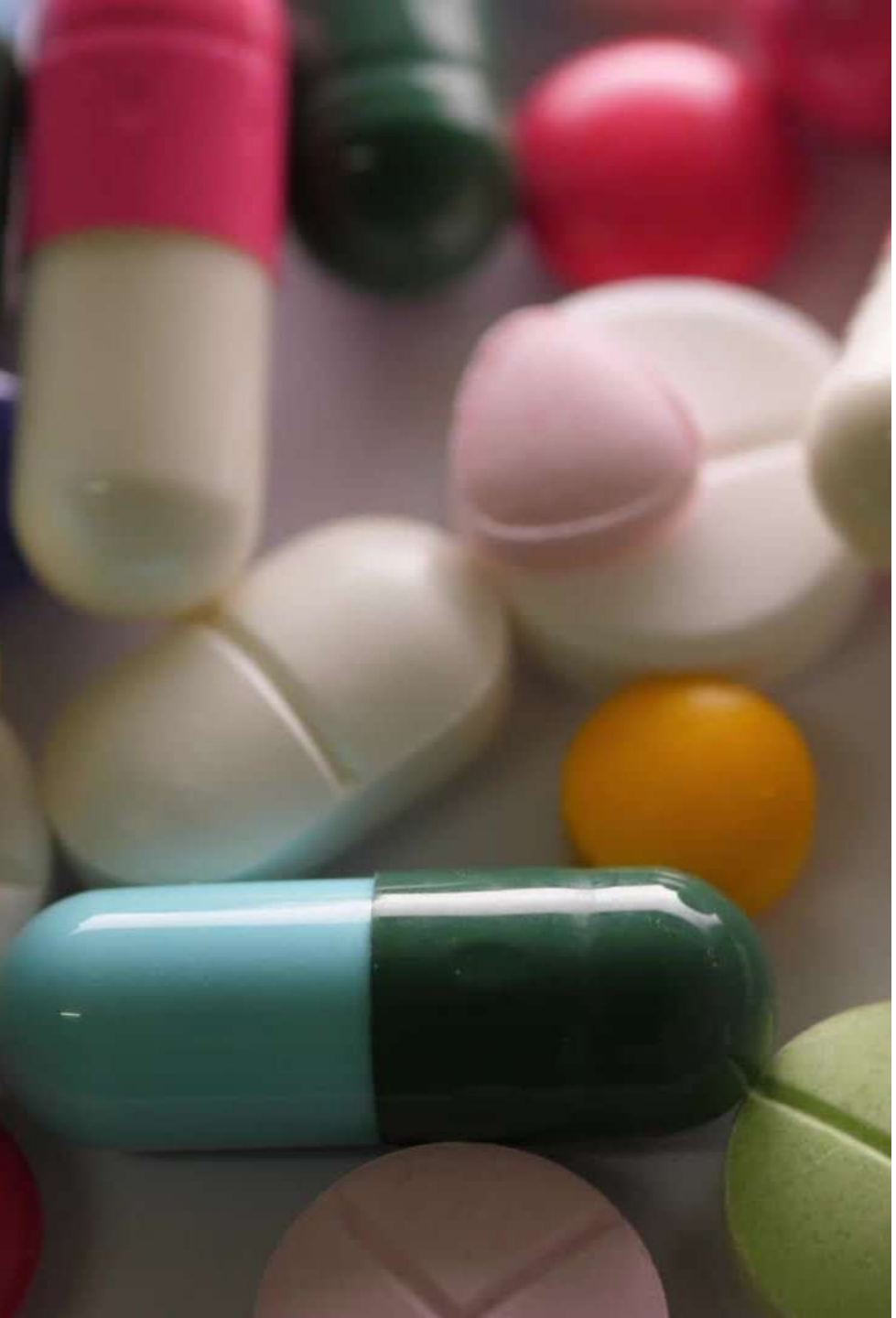
Abstract

Ubiquitous in nature, antimicrobial resistance (AMR) has existed long before the golden age of antimicrobials. While antimicrobial agents are beneficial to combat infection, their widespread use contributes to the increase and emergence of novel resistant microbes in virtually all environmental niches. The human microbiome is an important reservoir of AMR with initial exposure occurring in early life. Once seeded with AMR, commensal organisms may be key contributors to the dissemination of resistance due to the interconnectedness of microbial communities. When acquired by pathogens however, AMR becomes a serious public health threat worldwide. Our ability to combat the threat of emerging resistance relies on accurate AMR detection methods and the development of therapeutics that function despite the presence of antimicrobial resistance.

*İnsan barsağında:
10-100 Trilyon Mikrobiyal hücre
*Bir başka organa göre 150 kat daha fazla genetik heterojenite
*10^{14} mikrobiyal hücre sayısı
>400 bakteri türü
*En az 300 tür arasında 13.500 genetik aktarım
*Farklı ekosistemlere göre 25 kat fazla genetik hareketlilik



Diyabetik Ayak İnfeksiyonlarında Antibiyotik Başarısızlığı

- Biyofilm tabakasına etkisizlik
- Antibakteriyel direnç artışı
- Polimikrobiyal etkenlere yetersiz yanıt
- Antibiyotiklerin hedef dokuda subteröpatik düzeyde kalması
- Uzun süreli antibiyotik kullanımı gereksinimi
- MDR bakterilerle yeni kolonizasyon riskleri
- Antibiyotik tedavisine katkı sağlayacak immün yanıt eksikliği

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BMC Microbiology

RESEARCH ARTICLE Open Access

Efficacy of phage cocktail AB-SA01 therapy in diabetic mouse wound infections caused by multidrug-resistant *Staphylococcus aureus*

Legesse Garedew Kifelew[1,2*], Morgyn S. Warner[3,4], Sandra Morales[5], Lewis Vaughan[6], Richard Woodman[7], Robert Fitridge[8], James G. Mitchell[1] and Peter Speck[1]

Abstract

Background: Diabetic foot ulcer (DFU) is a serious complication of diabetes mellitus. Antibiotic-resistant *Staphylococcus aureus* is frequently isolated from DFU infections. Bacteriophages (phages) represent an alternative or adjunct treatment to antibiotic therapy. Here we describe the efficacy of AB-SA01, a cocktail of three *S. aureus Myoviridae* phages, made to current good manufacturing practice (cGMP) standards, and which has undergone two phase I clinical trials, in treatment of multidrug-resistant (MDR) *S. aureus* infections.

Results: Wounds of saline-treated mice showed no healing, but expanded and became inflamed, ulcerated, and suppurating. In contrast, AB-SA01 treatment decreased the bacterial load with efficacy similar or superior to vancomycin treatment. At the end of the treatment period, there was a significant decrease ($p < 0.001$) in bacterial load and wound size in infected phage- and vancomycin-treated groups compared with infected saline-treated mice. In phage-treated mice, wound healing was seen similar to vancomycin treatment. No mortality was recorded associated with infections, and post-mortem examinations did not show any evident pathological lesions other than the skin wounds. No adverse effects related to the application of phages were observed.

Conclusion: Topical application of phage cocktail AB-SA01 is effective, as shown by bacterial load reduction and wound closure, in the treatment of diabetic wound infections caused by MDR *S. aureus*. Our results suggest that topical phage cocktail treatment may be effective in treating antibiotic-resistant *S. aureus* DFU infections.

Keywords: Diabetic mice, Infection, MDR *S. aureus*, Phage cocktail, Treatment, Wound

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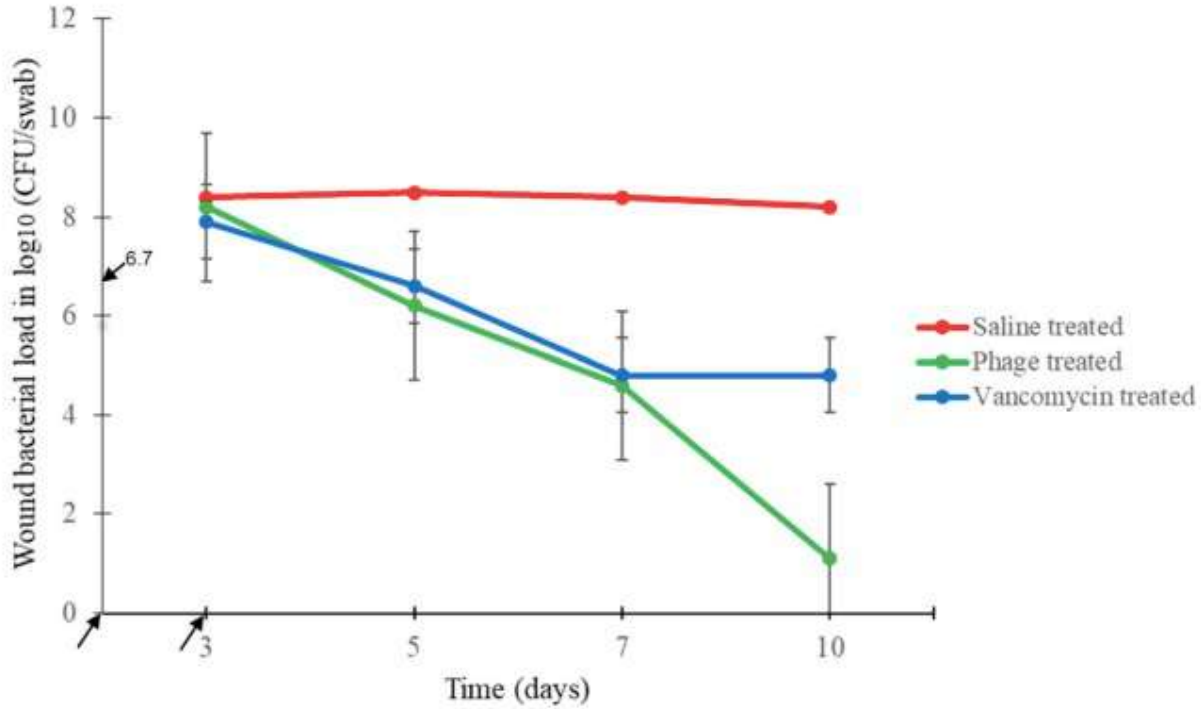

Fig. 1 Effect of phage treatment on *S. aureus* bacterial load compared to control and IP vancomycin treatment. Saline-treated mice (control, red); AB-SA01 phage-treated mice (green); vancomycin-treated mice (blue). No *S. aureus* was detected from uninfected phage-treated mice. The arrows on the horizontal axis indicate the infection date (first arrow, day 0) and treatment start date (second arrow, day 3), respectively. Treatments were applied from day 3 to day 7 of infection, as detailed in the text. The arrow on the vertical axis indicates the infection dose

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Table 1 Bacterial load (log_{10} CFU/swab) after treatments in diabetic mice wounds infected with MDR *S. aureus*

Mouse ID	Treatment group	Infection period				
		Day 0	Day 3	Day 5	Day 7	Day 10
4-NEM	Saline	0	8.99	8.36	8.51	8.57
4-1 L		0	7.72	8.11	8.43	7.91
4-2R		0	8.34	8.85	8.38	8.18
5-NEM		0	7.00	8.34	8.41	7.62
5-1 L		0	8.76	8.70	8.20	8.11
5-2R		0	6.97	7.73	8.51	8.53
10-RL		0	7.00	8.38	8.26	7.95
Mean ± err		0	8.42 ± 0.9	8.47 ± 0.4	8.39 ± 0.1	8.23 ± 0.3
7-1R	Phage	0	8.40	6.43	2.26	0.00
7-1 L		0	8.40	6.18	5.72	2.00
7-RL		0	7.88	6.45	6.30	2.28
7-2R		0	8.56	6.26	6.63	0.00
9-NEM		1.1	8.38	6.28	2.48	4.34
9-1R		1.5	8.81	6.45	5.15	0.00
9-1 L		0	8.41	5.80	5.72	0.00
9-RL		0	6.66	5.43	2.32	0.00
Mean ± err		0.3	8.19 ± 0.7	6.16 ± 0.4	4.57 ± 1.9	1.08 ± 1.6
6-1R	Vancomycin	0	8.64	6.18	5.15	7.04
6-RL		0	7.46	4.70	3.96	5.86
6-2R		0	8.04	7.99	4.75	6.75
8-NEM		0	7.84	6.49	5.58	1.04
8-1 L		0	7.80	6.52	4.28	6.04
8-2R		0	7.72	7.92	4.96	2.11
Mean ± err		0	7.92 ± 0.4	6.63 ± 1.2	4.78 ± 0.6	4.81 ± 2.6

Efficacy of phage cocktail AB-SA01 therapy in diabetic mouse wound infections caused by multidrug-resistant *Staphylococcus aureus*

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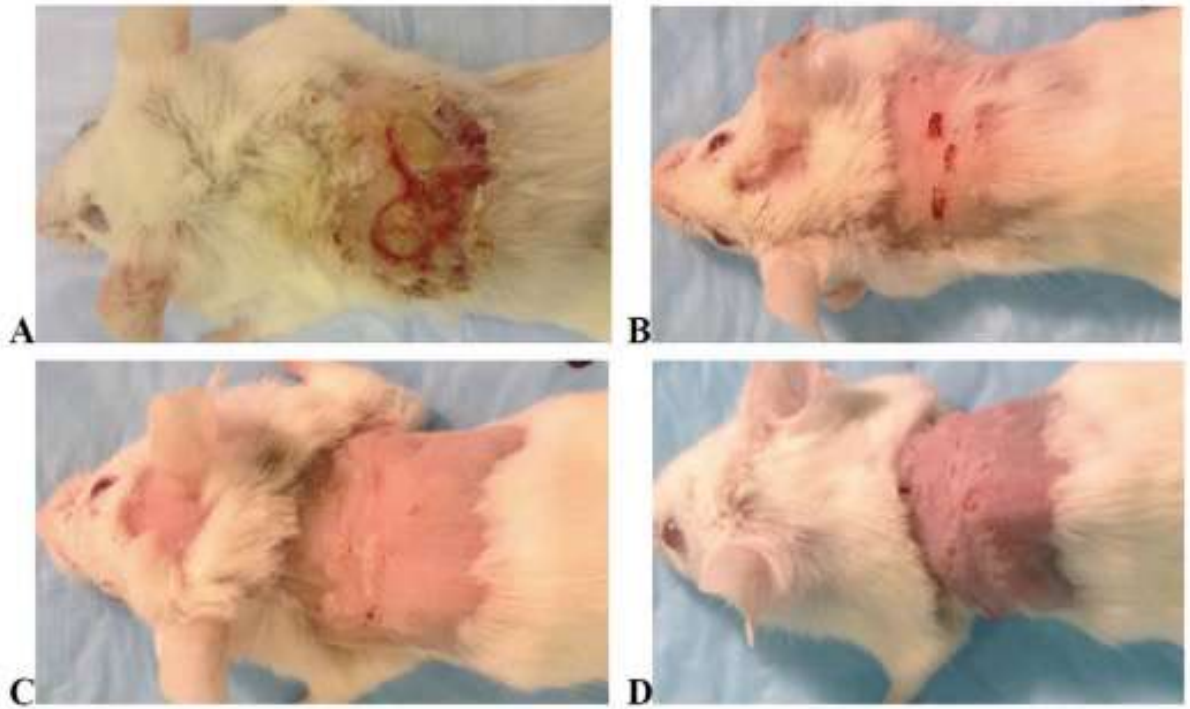

Fig. 2 Representative images diabetic mouse wound at day 10 of infection: **A** infected saline-treated, showing lack of healing and expansion of wounds; **B** uninfected phage-treated, **C** infected phage-treated, and **D** infected vancomycin-treated. Wounds in **B, C,** and **D** groups showed similar complete healing

- **Diyabetik Ayak İnfeksiyonlarının tedavisinde;**
- **Tek başına antibiyotik mi?**
- **Tek başına bakteriyofaj mı?**
- **Kombine tedavi mi?**

Fighting Pathogenic Bacteria on Two Fronts: Phages and Antibiotics as Combined Strategy

Thaysa Leite Tagliaferri [1,2]***, Mathias Jansen*** [1] ***and Hans-Peter Horz*** [1]*

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With the emerging threat of infections caused by multidrug resistant bacteria, phages have been reconsidered as an alternative for treating infections caused by tenacious pathogens. However, instead of replacing antibiotics, the combination of both types of antimicrobials can be superior over the use of single agents. Enhanced bacterial suppression, more efficient penetration into biofilms, and lowered chances for the emergence of phage resistance are the likely advantages of the combined strategy. While a number of studies have provided experimental evidence in support of this concept, negative interference between phages and antibiotics have been reported as well. Neutral effects have also been observed, but in those cases, combined approaches may still be important for at least hampering the development of resistance. In any case, the choice of phage type and antibiotic as well as their mixing ratios must be given careful consideration when deciding for a dual antibacterial approach. The most frequently tested bacterium for a combined antibacterial treatment has been *Pseudomonas*

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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

Department of Microbiology, Panjab 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 inflicted with drug resistant strains represent a morbid combination in diabetic patients. 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 alloxan induced diabetic BALB/c mice. Therapeutic efficacy of a well characterized broad host range lytic bacteriophage, MR-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.

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Department of Microbiology, Panjab University, Chandigarh, India

- Group 1: Diabetic mice were infected with *S.aureus* 43300(10^6 CFU/ml).
- Group 2: Diabetic mice were infected with *S.aureus* 43300 followed by administration of phage at a multiplicity of infection (MOI) – 100 [30 minutes post-infection].
- Group 3: Diabetic mice were infected with *S.aureus* 43300 followed by administration of linezolid (25 mg/kg/per oral).
- Group 4: Diabetic mice were infected with *S.aureus* 43300 followed by administration of phage at a MOI of 100 as well as simultaneous administration of linezolid (25 mg/kg/per oral).

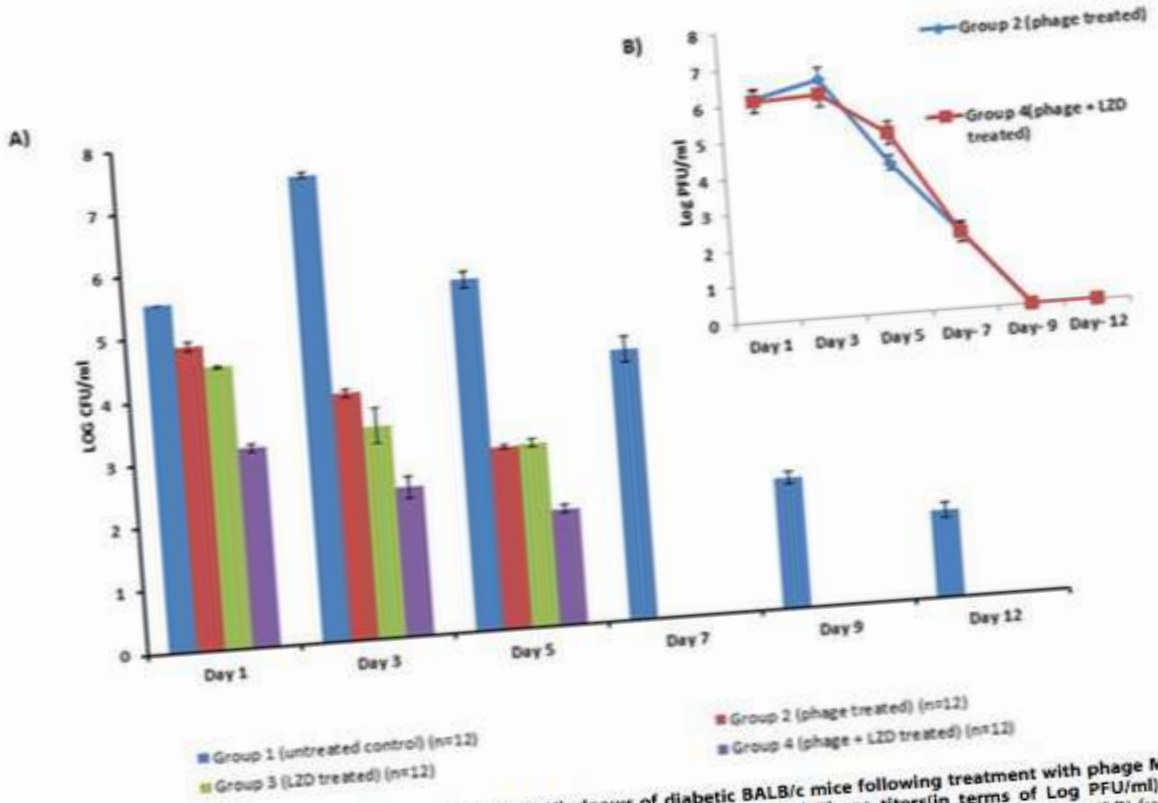

Figure 4. Bacterial load (in terms of Log CFU/ml) in A) Hindpaws of diabetic BALB/c mice following treatment with phage MR-10, linezolid and combination of phageMR-10 and linezolid (25 mg/kg/per oral) and Phage titers(in terms of Log PFU/ml) in B) Hindpaws of phage treated (group 2) and phage + LZD treated (group 4). [Error bars represent the standard deviation (S.D) from four independent values].
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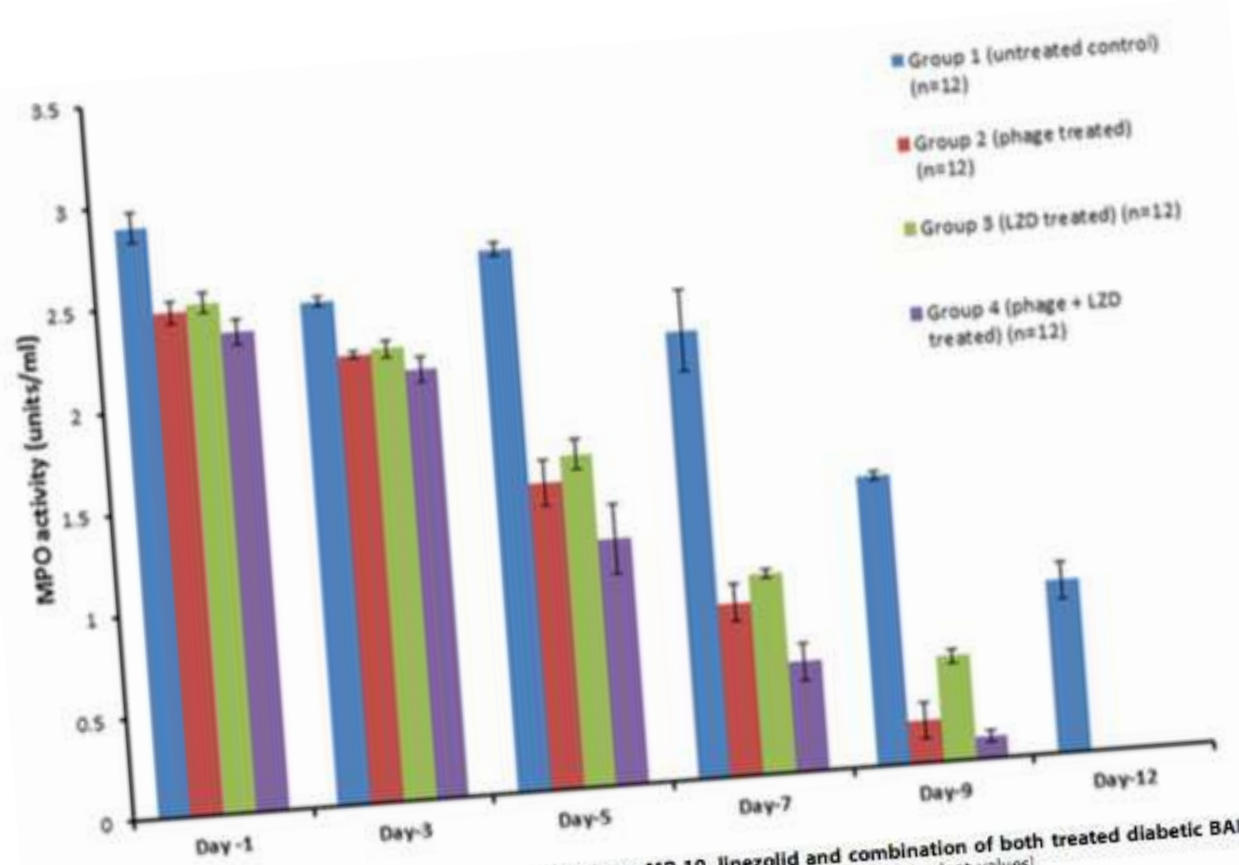

Figure 5. Comparison of MPO levels in the hindpaw of phage MR-10, linezolid and combination of both treated diabetic BALB/c mice at different time intervals. [Error bars represent the standard deviation (S.D) from four independent values].
doi:10.1371/journal.pone.0056022.g005

Fighting Pathogenic Bacteria on Two Fronts: Phages and Antibiotics as Combined Strategy

*Thaysa Leite Tagliaferri [1,2], Mathias Jansen [1] and Hans-Peter Horz [1]**

MDR Bakteri	Bakteriyofaj	Antibiyotik
Pseudomonas aeruginosa	NP1 (*Siphoviridae, NP1Virus*) ve NP3 (*Myoviridae*)	Seftazidim, Siprofloksasin, Tobramisin, Gentamisin
Klebsiella pneumoniae	KPO1K2 (*Podoviridae, T7-like virus*)	Siprofloksasin
Acinetobacter baumannii	vB_AbaM-KARL-1 (*Myoviridae*, *T4- like virus*)	Meropenem, Siprofloksasin, Kolistin
Staphylococcus aureus	SAP-26 (*Siphoviridae, Phietavirus*)	Vankomisin, Siprofloksasin, Amikasin
Escherichia coli	RB32 ve RB33 (*Myoviridae*) T4, T3 (*Podoviridae, T7virus*)	Sefotaksim Siprofloksasin
Burkholderia cepacia	KS12 (*Myoviridae*) and KS14 (*Myoviridae*, *P2-like virus*)	Minosiklin, siprofloksasin, meropenem

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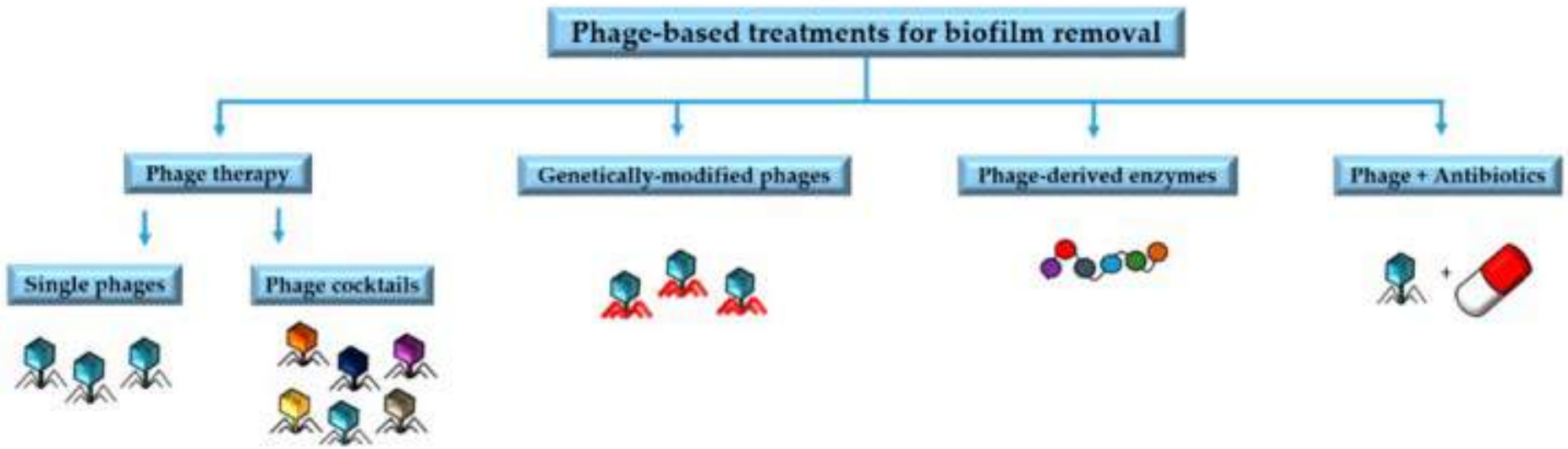
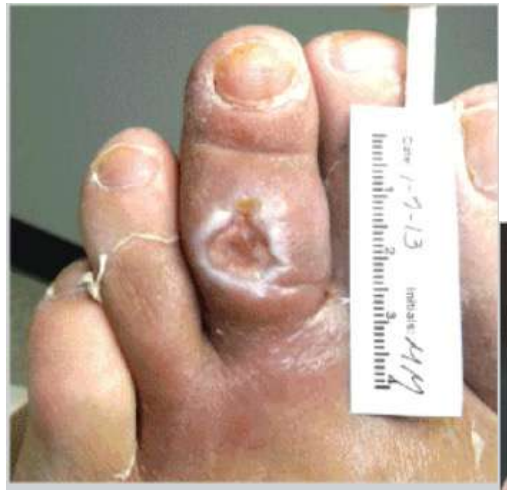
Abstract: Biofilms are clusters of bacteria that live in association with surfaces. Their main characteristic is that the bacteria inside the biofilms are attached to other bacterial cells and to



Olgularla Bakteriyofaj Tedavileri

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



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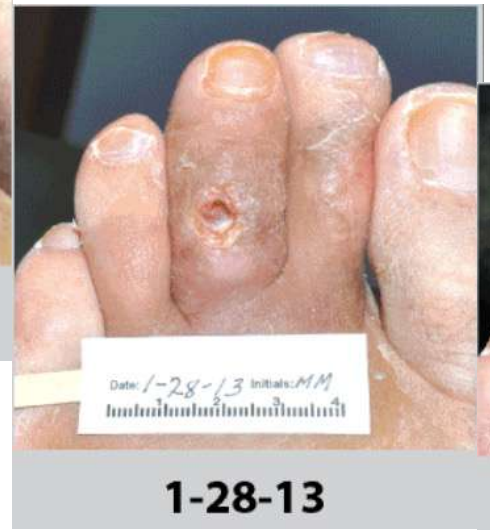

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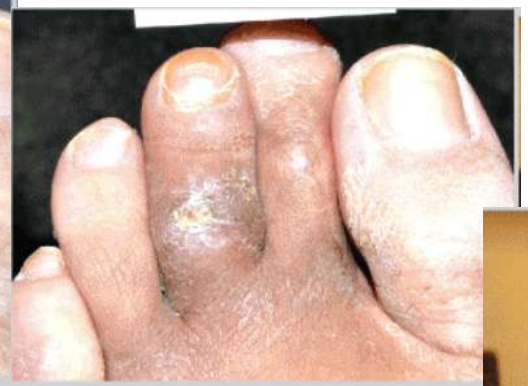
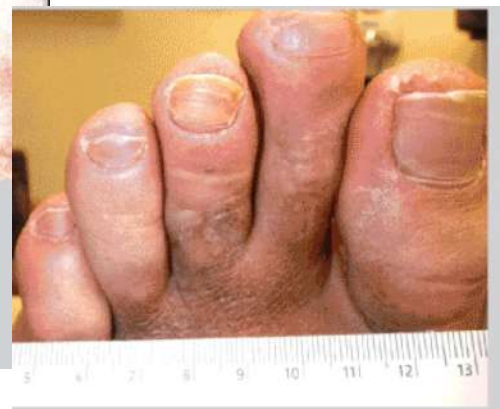


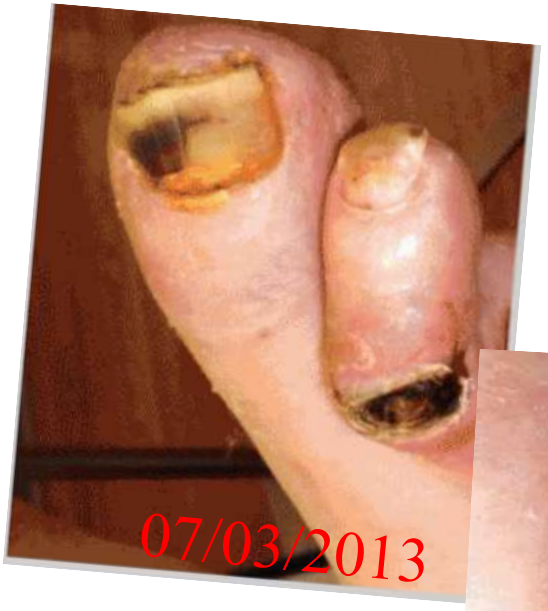
2-25-13
Wound closed

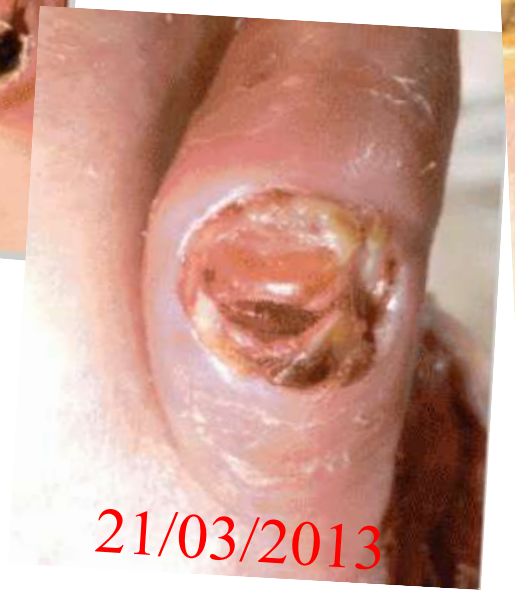


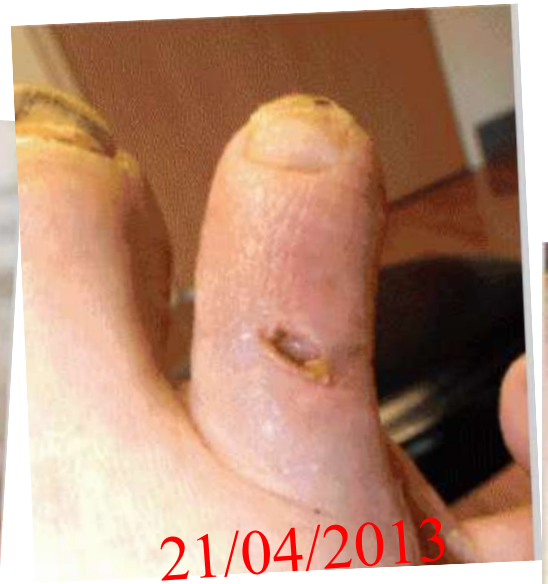
3-18-14
Wound remains closed after 1 year

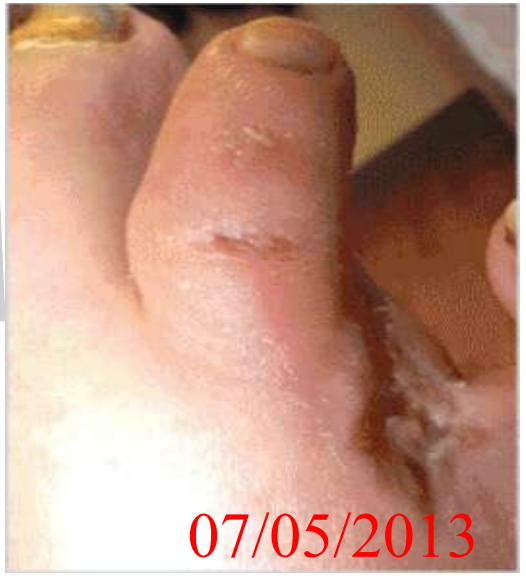
Olgularla Bakteriyofaj Tedavileri

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





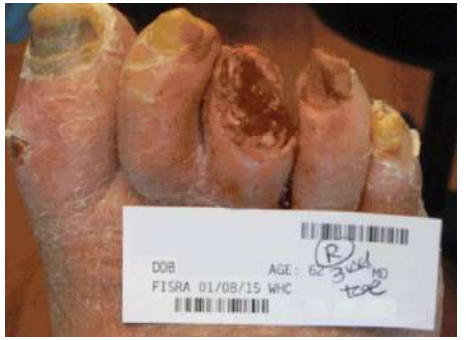




Olgularla Bakteriyofaj Tedavileri

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

07/03/2013



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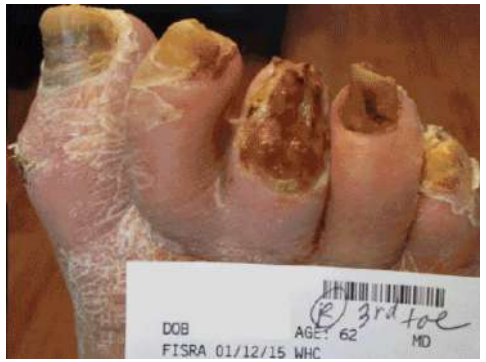
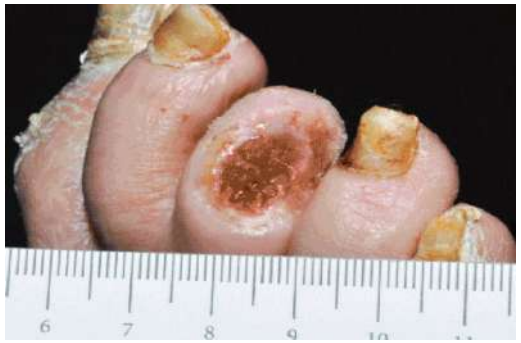


21/03/2013



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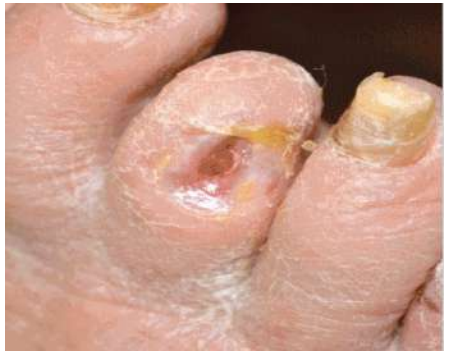

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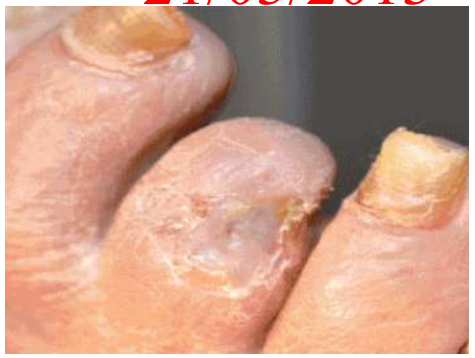

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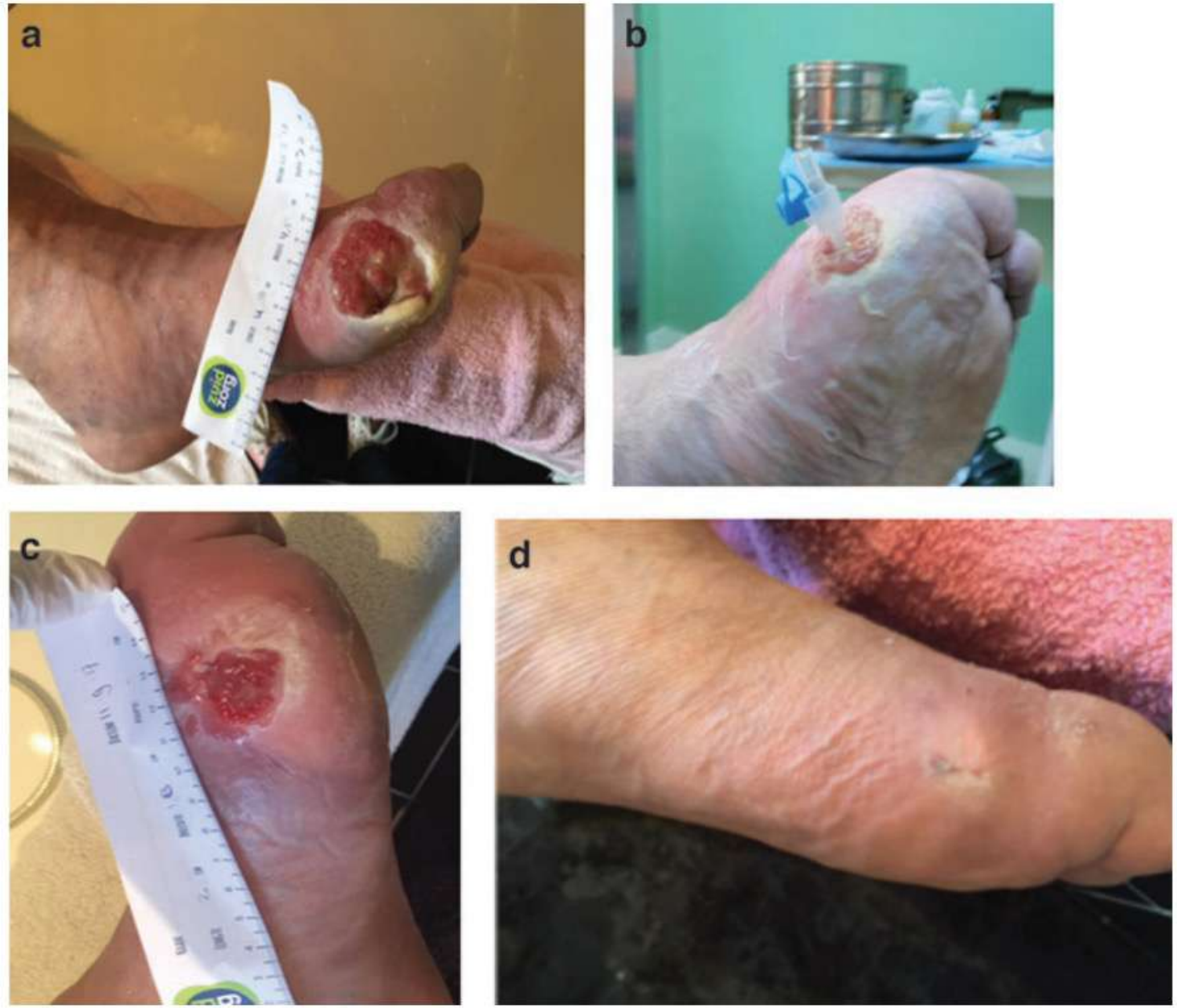


FIG. 3 **(a)** Before treatment, on the left toe, diabetic foot ulcer is seen. The wound is 5 cm in diameter. **(b)** Catheter is placed into the ulcer for direct application of phages into the tissue. **(c)** Six weeks after treatment; the size of the wound reduced to 2 cm by 1.8 cm. **(d)** Post-bacteriophage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

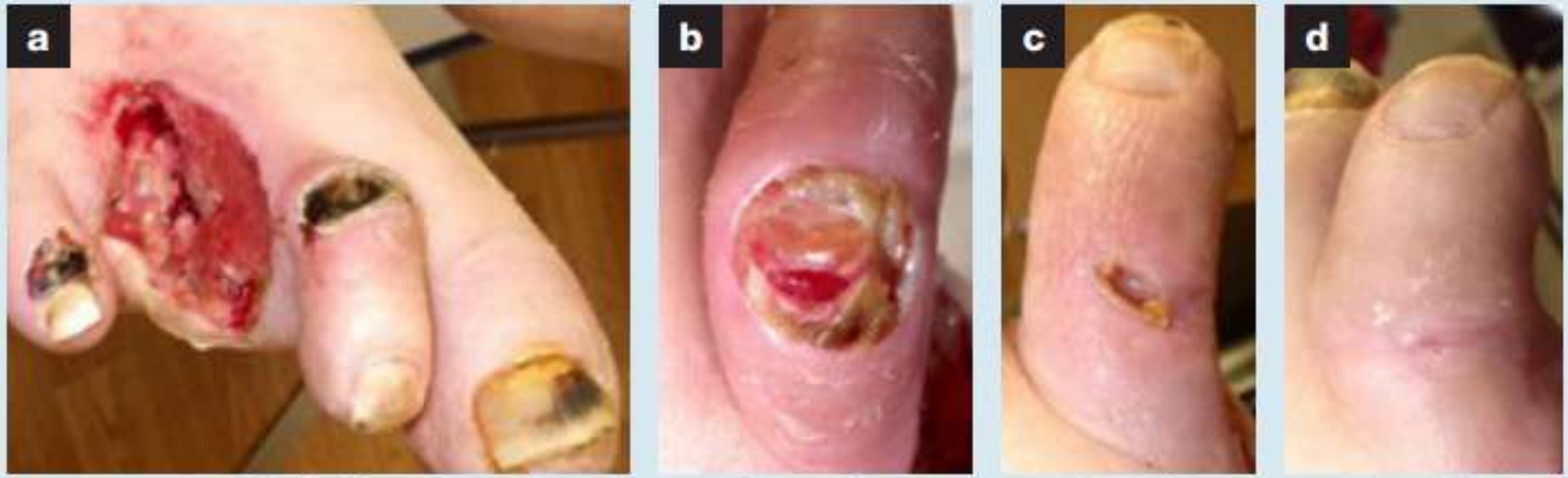


Fig 2. Patient 2. A 92-year-old male with contracted toe and shoe injury. The base of the middle phalanx was exposed in the centre of the and was excised

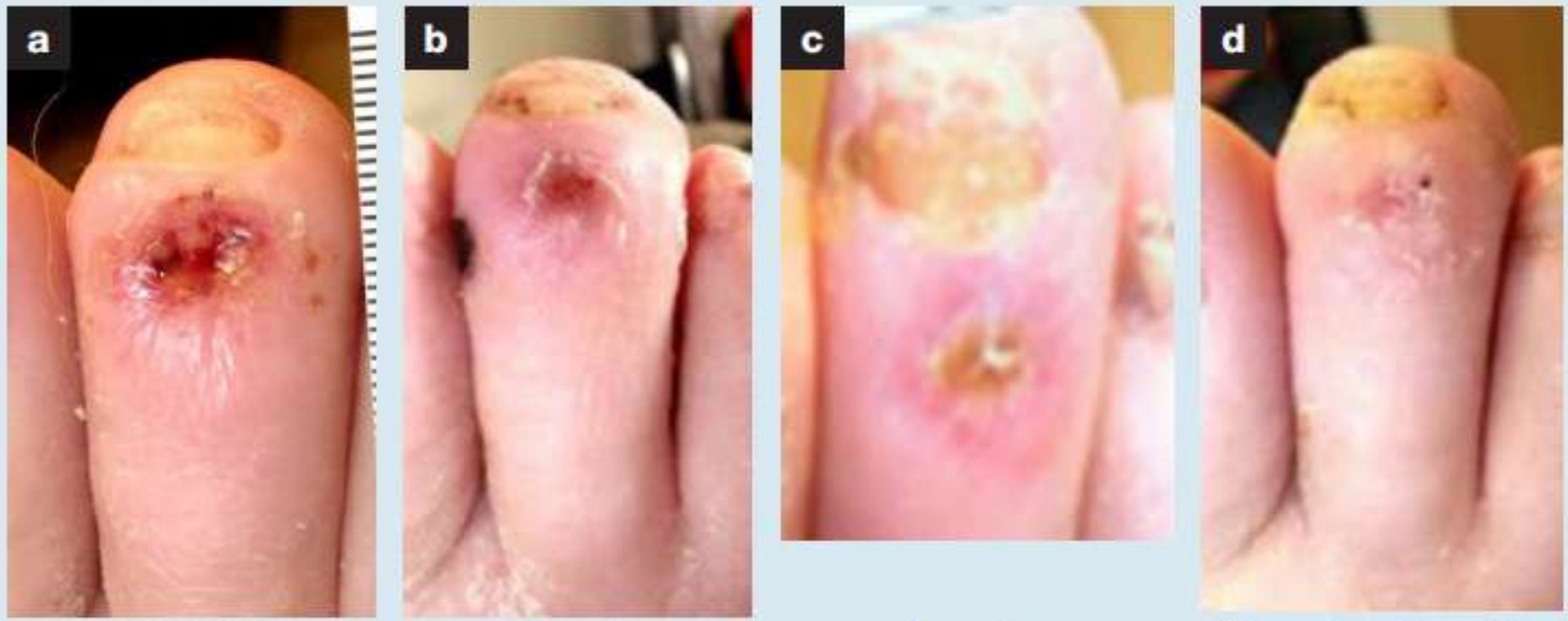
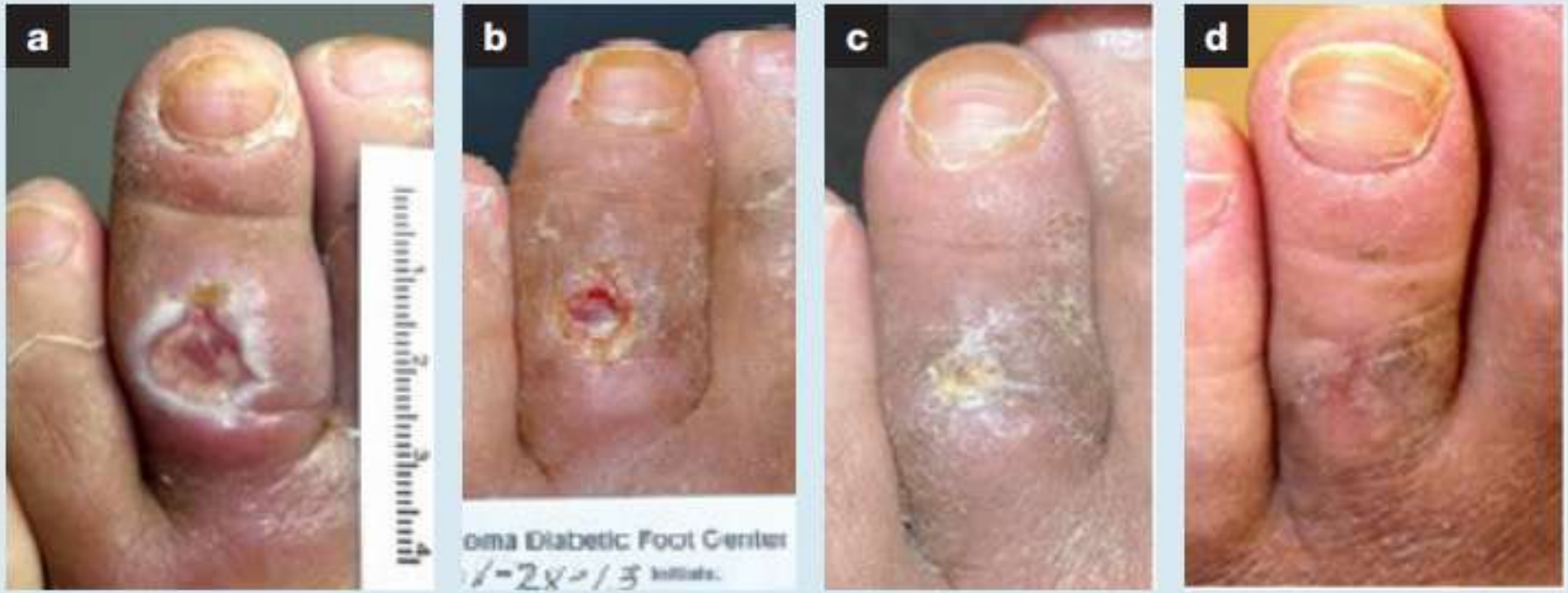


Fig 3. Patient 3. A 48-year-old male with diabetes and a resolved ulcer and cellulitis. The toe remained healed after 1 year



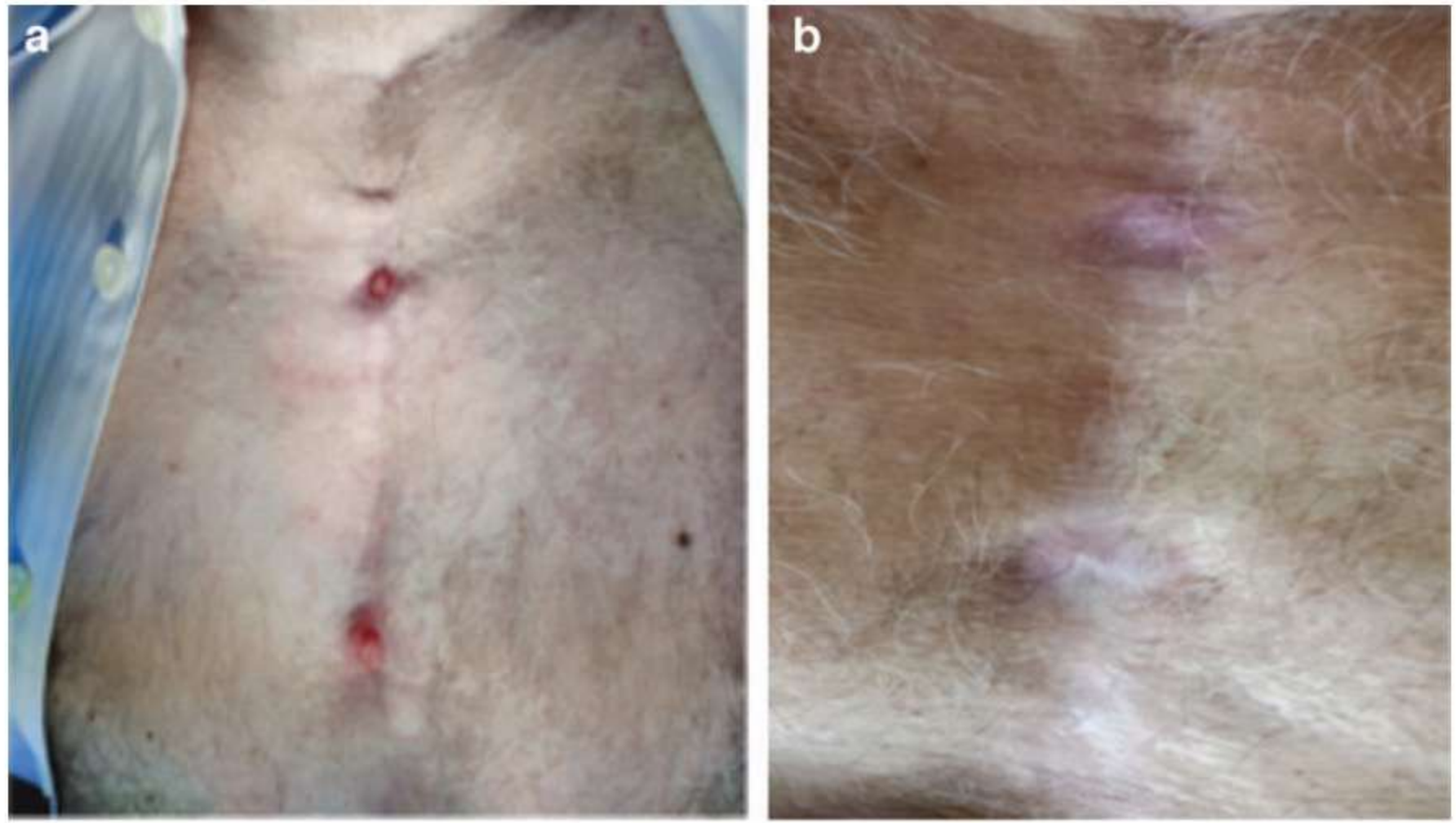


FIG. 1 **(a)** The image was taken on admission. Two purulent fistulas are seen in the sternal bone. The diameter of the upper fistula is 0.6 cm and the diameter of the lower fistula is 0.4 cm. **(b)** Postbacteriophage treatment, the fistulas have closed and there is no purulent exudate.

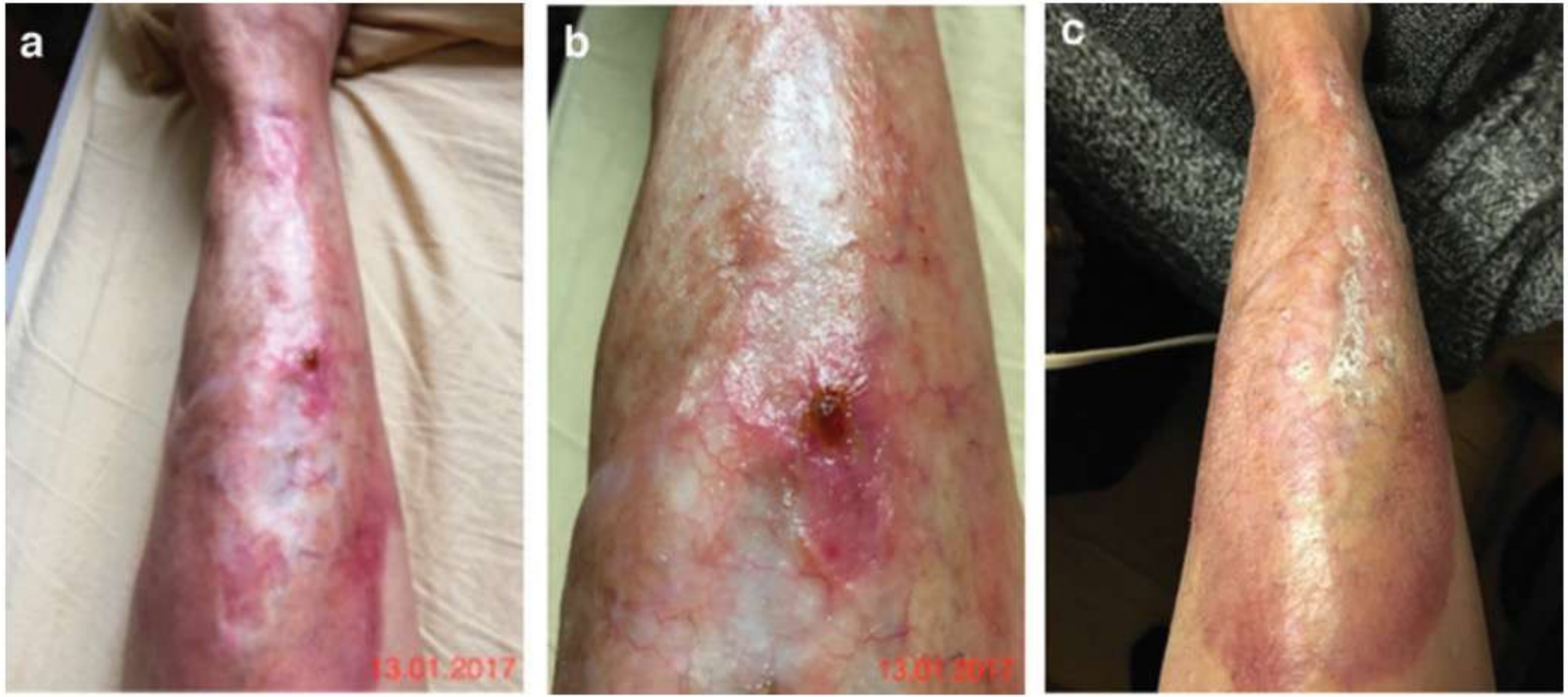
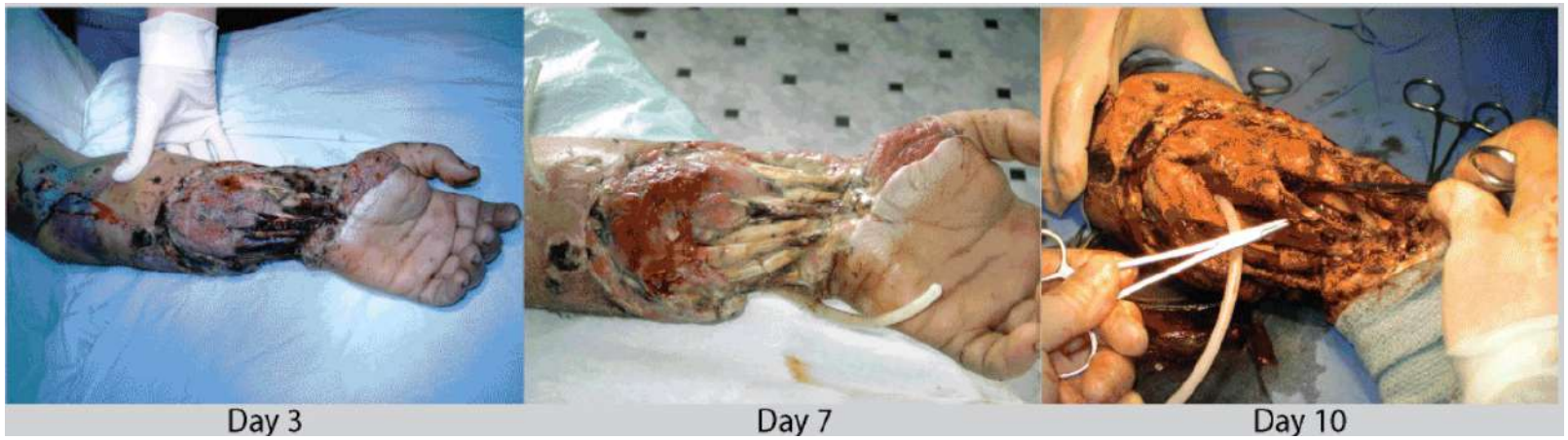


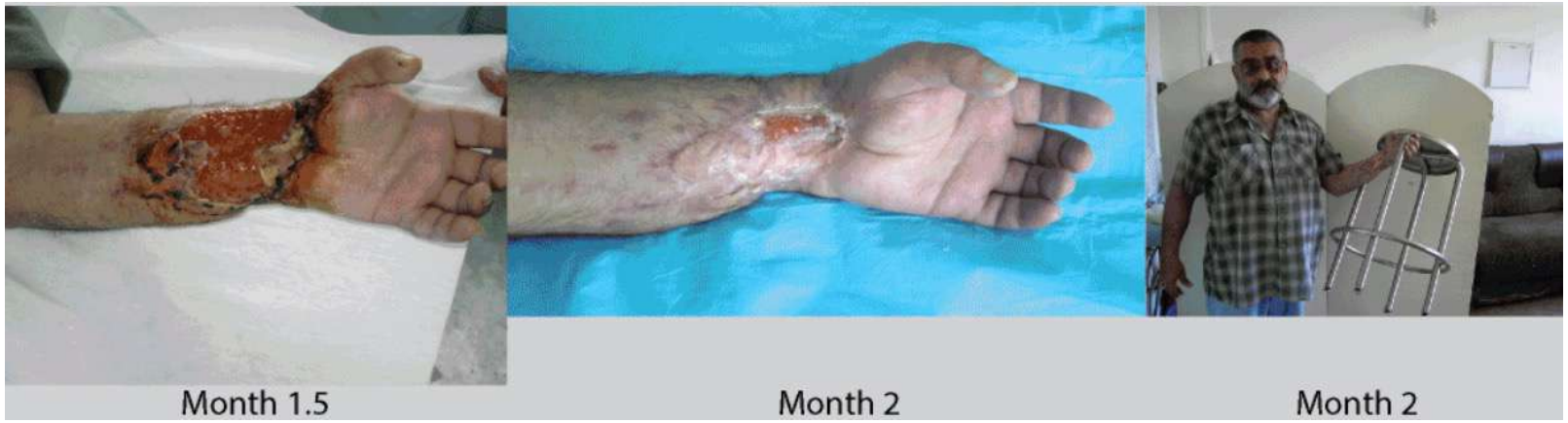
FIG. 2 **(a)** Pretreatment, the skin on the bone is markedly red, delicate, and fragile. **(b)** Purulent ulcer is visible. **(c)** Post-treatment, the color of the skin has changed from red to pink. The ulcer has filled in completely.

Olgularla Bakteriyofaj Tedavileri

- Tiflis, Gürcistan
- 55 yaş erkek,
- Maden işçisi
- Patlayıcıya maruziyet
- 12 ay IV AB tedavi
- Debritman..
- Amputasyon önerileri



- Bakteriyofaj tedavisi..



Wound Repair and Regeneration

Wound healing potential of topical bacteriophage therapy on diabetic cutaneous wounds

João J. Mendes, MD[1,2]; Clara Leandro, MSc[1]; Sol
Patrícia Cavaco-Silva, PharmD, PhD[1,4]; José Melc
Miguel Garcia, PharmD, PhD[1]

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Accepted in final form: March 18, 2013

DOI:10.1111/wrr.12056

ABSTRAC

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INTRODUCTION

Diabetic foot infections (DFIs) are a frequent and
complication of diabetes mellitus (DM) and are the
leading cause of nontraumatic lower limb amputat
current clinical practice, DFI treatment includes debr
and systemic antibiotics.[2] However, because of
vascularization and insufficient local antibiotic co
tions, these treatments are often ineffective.[3] In
multidrug-resistant organisms, such as methicillin-
Staphylococcus aureus and pan-drug-resistant nonfe
Gram-negative bacilli, threaten the efficacies of the
pies in both community-dwelling and hospitalized p
Thus, it is necessary to identify new therapeutic strat
DFIs. Topical treatment is advantageous because
adverse effects from systemic treatment, increases t
concentration, and allows the use of agents that are
able for systemic therapy. Mechanical debridement
pivotal to this strategy because it significantly re
bioburden, and as elegantly demonstrated by Wolc
opens a time-dependent therapeutic window for to
microbial therapy (TAT). Nevertheless, no TAT
been proven to effectively treat DFI to date.[3]
Bacteriophages are small viral entities, existing
acids packaged within a protein capsid, that specific

NRC Research Press

REVIEW

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

Ayman El-Shibiny and Salma El-Sahhar

Abstract: Since their discovery in 19[1]5
humans because of their unique abil
populations. The research carried out
and Poland, led to the establishmen
sulfonamide antibiotics in the West
therapy. The misuse of antibiotics ha
in the number of antibiotic-resistant
of interest with the emergence of mu
have indicated that bacteriophages
agents. Moreover, they can be used
design, and in the nanomedicine fi

Key words: bacteriophages, antibiot

Résumé : Les bactériophages ont
depuis leur découverte en 19[1]3, à
affecter les autres populations bac
principalement en Géorgie, dans
thérapeutiques à partir de phages
cours des années 1930 a retardé l
depuis leur découverte a résulté e
réduction de leur efficacité à c
d'intérêt comme alternative aux
menace à la santé publique. Des
ement pour détecter les bactéri
peuvent être utilisés pour dével
vaccins, dans la conception de
[Traduit par la Rédaction]

Mots-clés : bactériophages, anti

Introduction

Bacteriophages are small viruses that h
to infect bacteria. They have a huge infl
environment, as they play a vital role in
microbial balance. Phages are ubiquitou
found in all the natural habitats, includi
terrestrial systems, in which their bact
present. Over 6000 different phages have
and described morphologically (Ackermann
2012). They can be classified on the basis
ogy, genetic content, host, habitat, or

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A. El-Shibiny and S. El-Sahhar. University
12588, Giza, Egypt.
Corresponding author: Ayman El-Shibin

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Cite this as: Swiss Med Wkly. 2017;147:w14553

Multidrug resistant (or antimicrobia pathogens - alternatives to new an

Brunel Anne-Sophie, Guery Benoit

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

Summary

For the last few decades, multidrug resistance has be-
come an increasing concern for both Gram-positive and
Gram-negative bacteria. The number of new molecules
has dramatically decreased and antibiotic resistance is
now a priority in the international community. Facing this
new threat, a large number of new as well as "old" solu-
tions are now being discussed in the medical community
to propose an alternative to antibiotic treatments. A first
option is to potentiate the affect of existing molecules
through combinations to circumvent the individual mole-
cule resistance. The second option is to neutralise either
the infectious agent itself or its by-products using specific
antibodies. A third option is to use the pathogen signaling
mechanism and inhibit the production of virulence factor
through quorum sensing inhibition. A fourth pathway
would be to interact with the patient's microbiota using ei-
ther probiotics or faecal transplantation to modulate the in-
nate immune response and improve response to the infec-
tious challenge, but also to act directly against colonisation
by resistant bacteria by replacing the flora with suscepti-
ble strains. The last option is to target the bacteria using
phage therapy. Phages are natural viruses that specifically
infect target bacteria independently of any antibiotic-sus-
ceptibility 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 treat-
ments represent an interesting approach but not the ul-
timate solution to multiresistance. Well-performed clinical
trials are still missing and the major priority remains to pre-
mote good use and appropriate stewardship of antibiotics
to decrease resistance.

*Key words: microbiota, phage, probiotics; quorum sens-
ing*

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 ob-
vious consequence was the rapid emergence of resistance
associated with the use of each new agent. Today, the num-
ber of antibiotic molecules is reaching a plateau, but resis-
tance continues to grow. In 2013, the United States Centers

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The Journal of Infectious Diseases

BRIEF REPORT

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

Jean-Philippe Rasigade,[1,2] Catherine Dunyach-Rémy,[3,4] Anaïs Sapin,[1] Nourredine Messad,[4] Sophie Trouillet-Assant,[1] Céline Dupieux,[1,2] Jean-Philippe Lavigne,[3,4] and Frédéric Laurent[1,2,4]

[1]INSERM U1111, International Center for Infectiology Research, Ecole Normale Supérieure de Lyon, CNRS UMR5308, [2]Institut des Sciences Pharmaceutiques et Biologiques de Lyon, University of Lyon, [3]National Reference Center for Staphylococci, Institute of Infectious Agents, Lyon University Hospital, [4]INSERM U1047, Faculty of Medicine, University of Montpellier, and [5]Department of Microbiology, University Hospital Carémeau, Nîmes, 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 uninfected 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 intracellular growth; diabetic foot infection; osteomyelitis; osteo

Staphylococcus aureus is both a frequent colonizer of h
and a versatile pathogen able to elicit invasive infection.
standing the mechanisms that drive the transition of *S*
from commensality to invasiveness is important to pr
fection risk in colonized patients and to propose tar
colonization procedures to high-risk patients. Alth
molecular epidemiology of carriage and clinical stra
markedly different [1], no genomic characteristic ab
discriminate commensal and invasive isolates has be
so far [2]. In particular, the presence of toxin-encod
the constitutive overexpression of toxins in certain
eages has been unambiguously associated with an i
ulence, based on epidemiological and experiment
these so-called hypervirulent *S. aureus* line

Received 28 June 2016; accepted 8 September 2016; published onli
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The Journal of Infectious Diseases® 2016;214:1605–8

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S. aureus
negative (Δrosa) variant have
NSA1385 was isolated from an uninfected DF

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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

Department of Microbiology, Panjab 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 inflicted with drug resistant strains represent a morbid combination in diabetic patients. 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 alloxan induced diabetic BALB/c mice. Therapeutic efficacy of a well characterized broad host range lytic bacteriophage, MR-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.

Citation: 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(2): e56022. doi:10.1371/journal.pone.0056022

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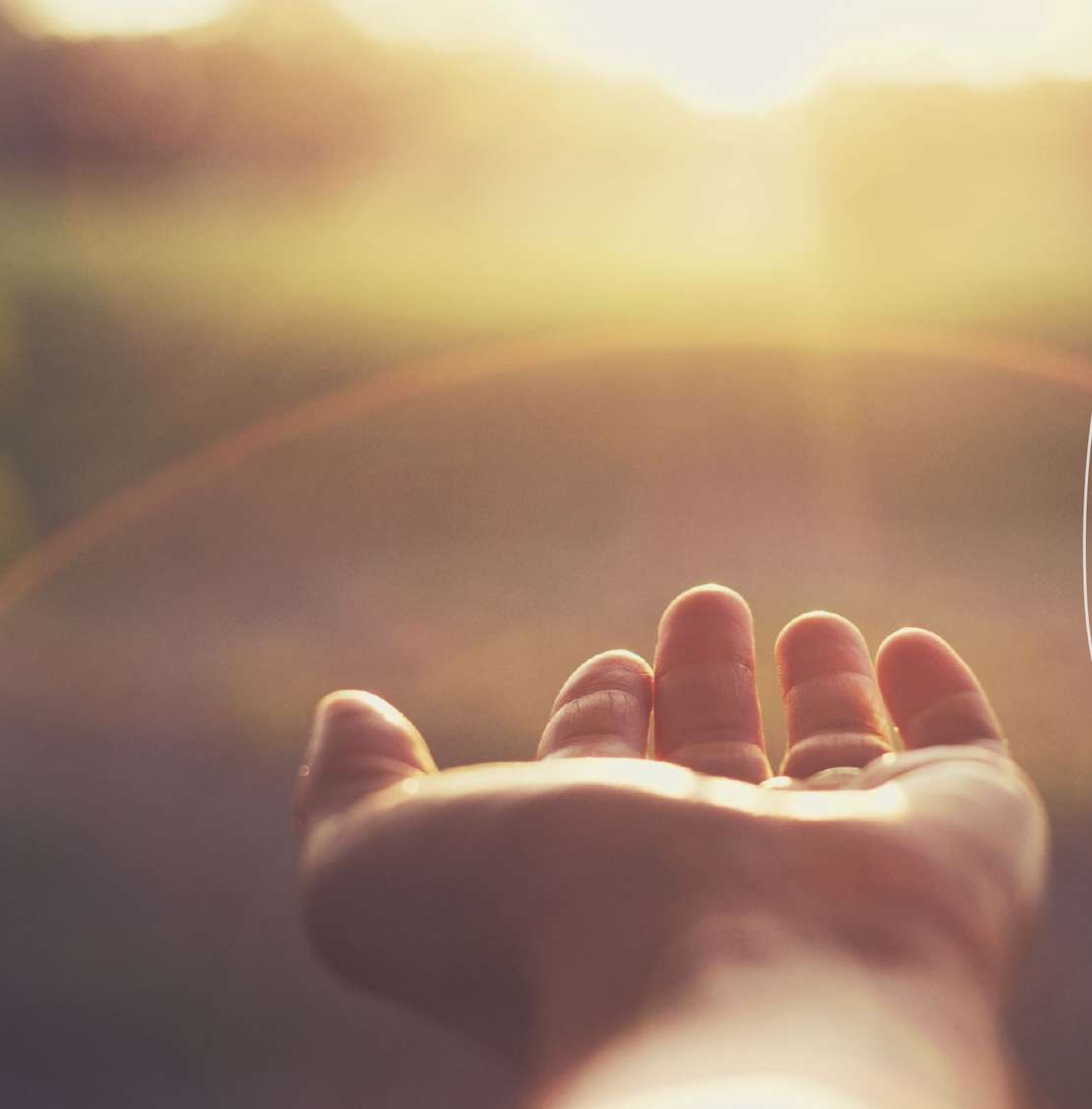
Introduction

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 to play in the development of foot infections. Wounds leading to foot and leg amputation occur in about 30 to 50 percent of patients with diabetes [3].

One of the most common pathogen in acute, previously untreated, superficial infected foot wound in patients with diabetes is *Staphylococcus aureus*. Overuse of antibiotics and the selection of broad- rather than narrow-spectrum agents has contributed towards 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 noticed in its incidence in many countries [5]. A recent study from Manchester 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 diabetics with foot infections 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 infections caused by MRSA undergoing amputation (43% MRSA vs 9% non-MRSA) [8].

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

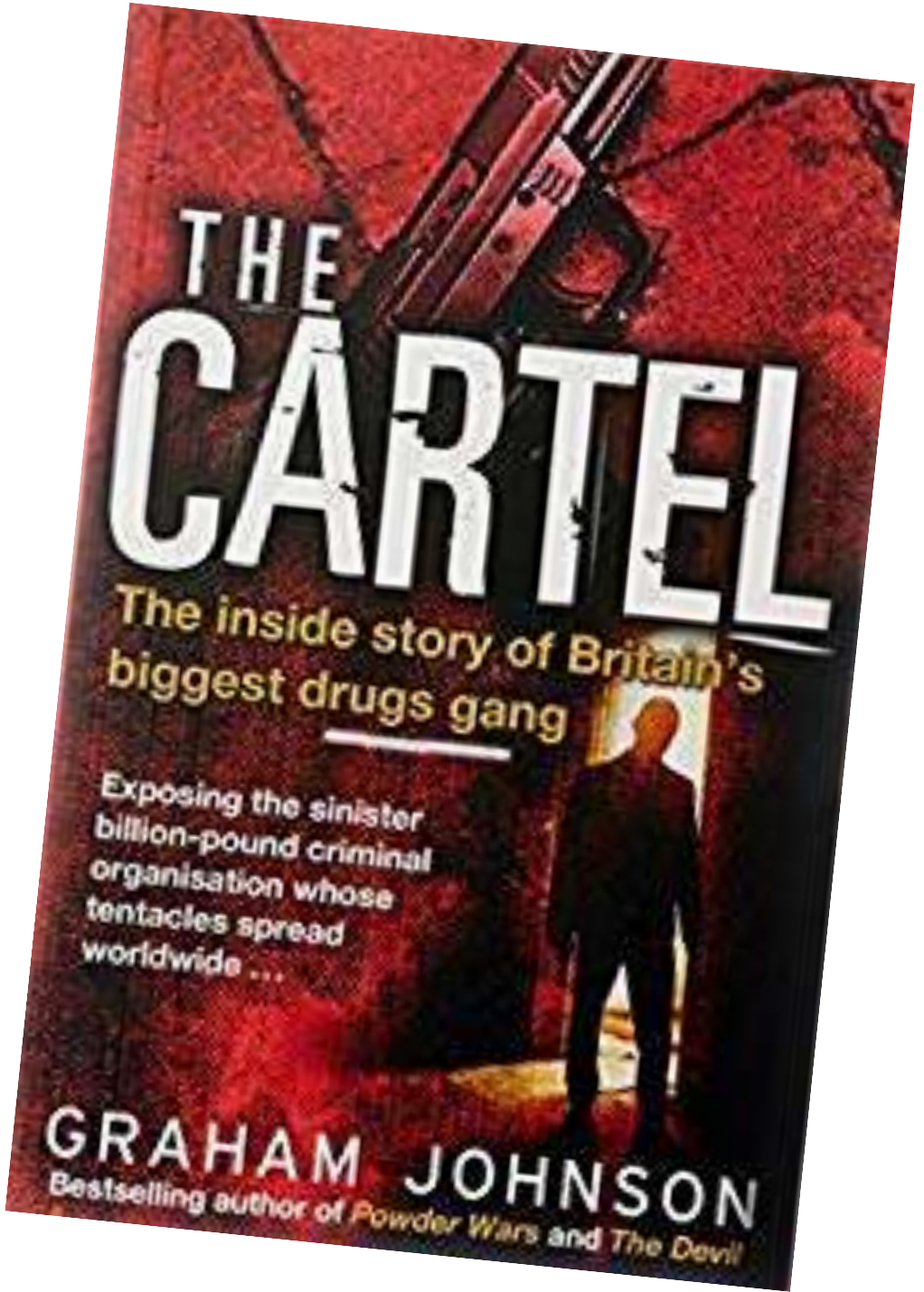


Neden Fajlarda Direnç Gelişmez

- Bakterilerle birlikte evrimleşirler
- Etkili bir faj, özgül bakteriyi tamamen yok edene kadar infekte eder
- Bakterinin genetik yapısını kullanarak direnç gelişimine izin vermez
- Endolizin her durumda peptidoglikan tabakayı parçalamaktadır
- Bakteri yüzeyel determinantları değiştirse bile yeni virionlara hedef olur

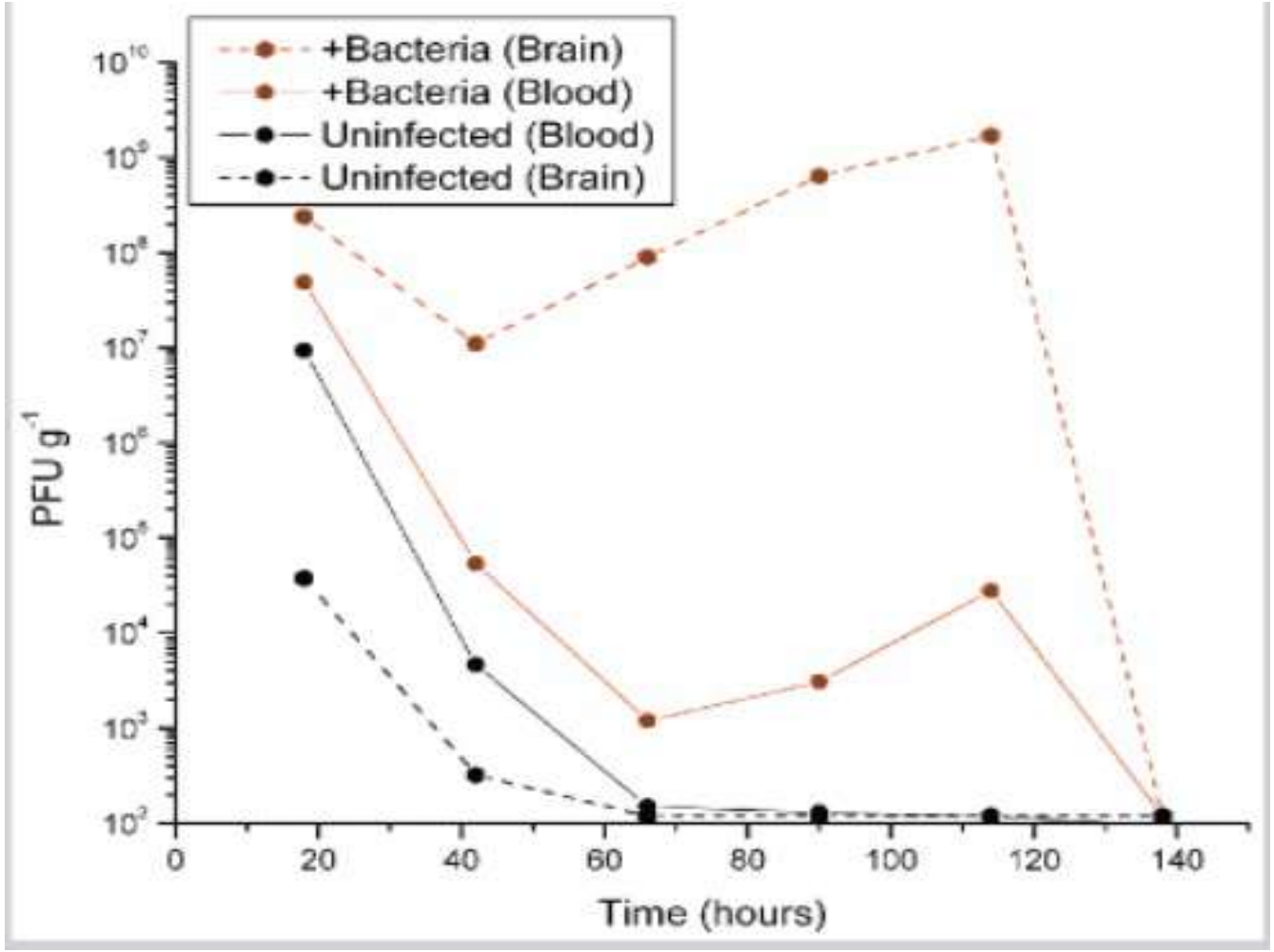
Klinik Kullanımı Neden Yaygınlaşmadı?

- Batıda kullanılmamasının birkaç nedeni var:
- Antibiyotiklerin yapımı, depolanması ve kullanımı daha pratik ve kolaydı
- Fajla ilgili çeşitli medikal girişimler yapıldı, sistemik kullanımını geliştirecek ARGE bütçeleri yeni antibiyotiklere kaydırıldı,
- Antibiyotik direnci henüz sorun olmadığından bakteriyofaj tedavisi önemini kaybetti
- İlaç firmaları için Antibiyotik geliştirmek ve buna dönük ARGE yatırımları daha karlı ve prestijli idi
- Uluslararası alanda Eski Sovyetler Birliği'nde gerçekleştirilen ve Rusça ya da Gürcü diliyle yazılan makaleler yeterince anlaşılamadı ve geniş okuyucu kitlesine ulaşmadı.



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..
- Bakteri eradikasyonundan sonra bakteriyofajların kaybı..



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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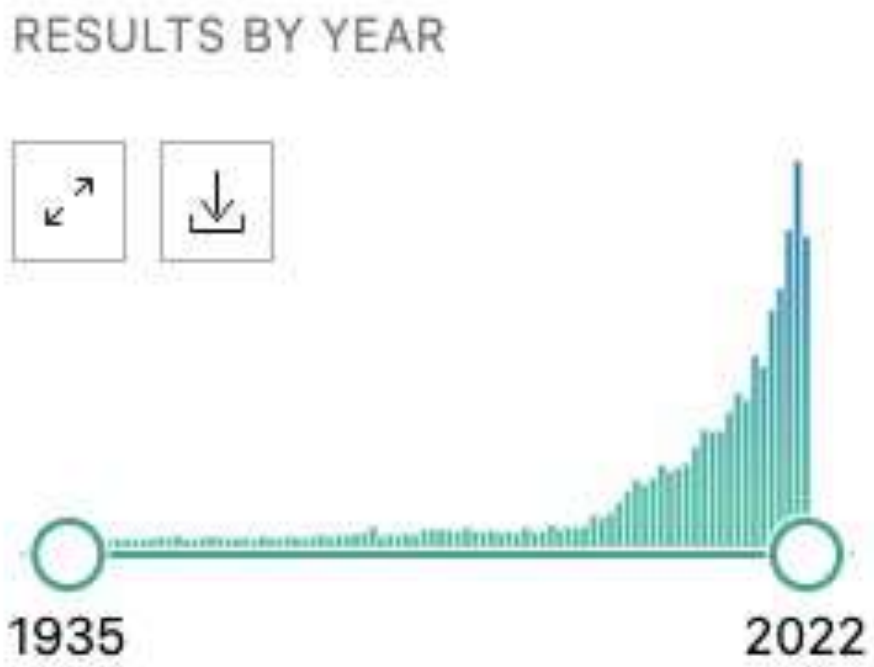
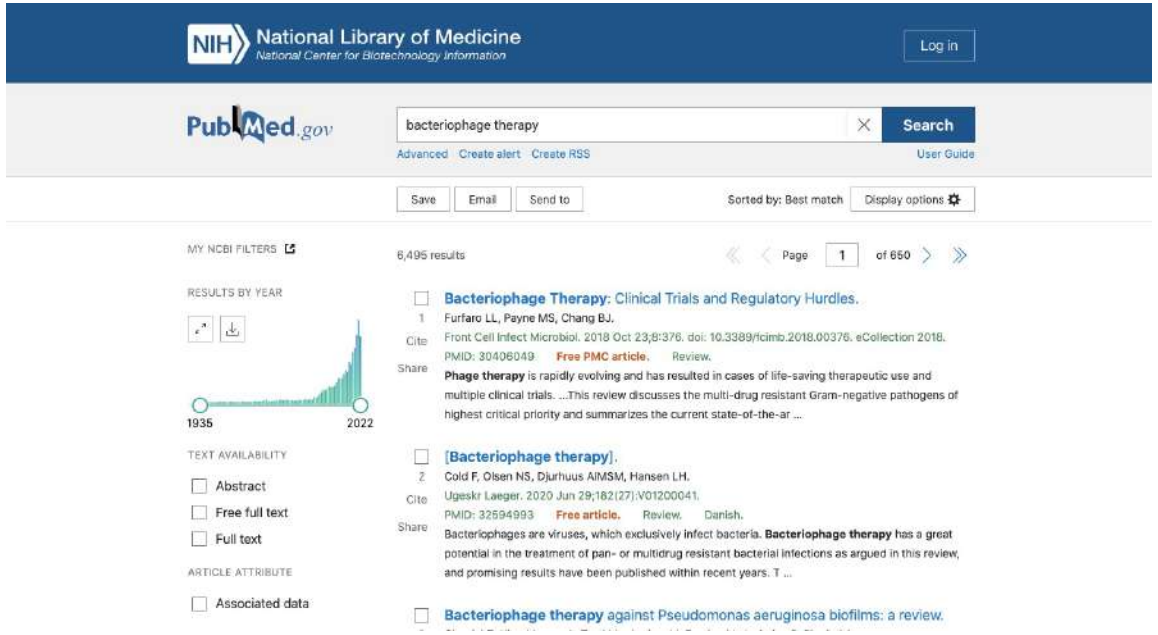
check for updates

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)

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 Olarak..

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TEŞEKKÜRLER..