



European
Knee
Society



HCL
HOSPICES CIVILS
DE LYON

New strategies

S. Lustig, C. Batailler, T. Ferry

Croix Rousse Hospital, Lyon, France

IFSTTAR, LBMC, Université Claude Bernard Lyon 1, Lyon, France

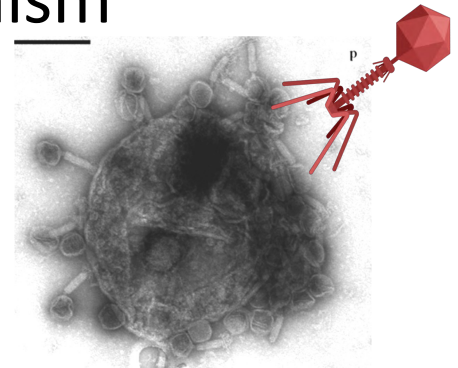


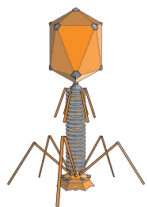
What is a « bacteriophage »?

- Suffix –phage, *phagos* φαγεῖν (*phagein*), "to eat", "to devour"

=> **Viruses (DNA or RNA) that infect bacteria**

- Largely abundant in the biosphere: 10³¹ bacteriophages on the planet, more than every other organism
- Especially in marine environment, sea, lake, backwater, soil, animal and human stools, etc.





History



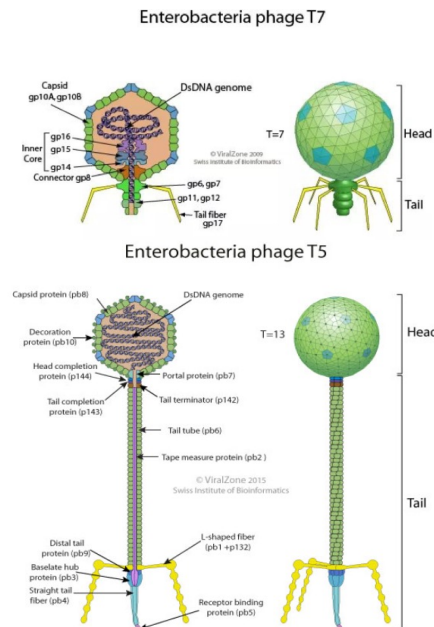
Ernest Hanbury Hankin
Reported in 1896

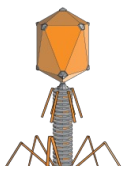


Frederick Twort
Discovered in 1915



Félix d'Hérelle
The First Clinical
Application in 1919

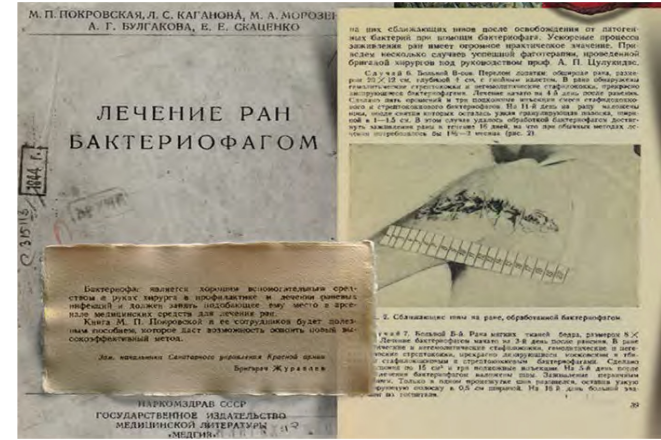




History



Figure 1. (A) Felix d'Herelle and George Eliava working at the bacteriophage institute in Tbilisi in the 1930s. (B) The George Eliava Institute of Bacteriophages, Microbiology, and Virology. (Courtesy of the Eliava Institute)



LE LABORATOIRE DU BACTÉRIOPHAGE
Laboratoire de recherches dont les bénéfices sont destinés à des fins scientifiques
sous le contrôle du
PROF. d'HERELLE

Bacté-coli-phage
Colibacilluries, Pyelonephrites, Cystites

Bacté-rhino-phage
Grippe, Coryza, Rhino-pharyngites

Bacté-intesti-phage
Enterites, Colites, Diarrhées infantiles

Bacté-pyo-phage
Panaris, Phlegmons, Plaies infectées

Bacté-staphyphage
Furonculose, Anthrax

AGENTS GÉNÉRAUX
LABORATOIRES ROBERT & CARRIÈRE - 37, rue de Bourgogne - Paris

BACTÉ-STAPHY-PHAGE

BACTÉ-PYO-PHAGE

LE LABORATOIRE DU BACTÉRIOPHAGE
FONDÉ PAR LE PROF. F. D'HERELLE
P. 30, RUE COURNEAU DE JARVIS - PARIS 17^{ème}
Tél. : Wagram 28-42

Le Journal de Médecine de Lyon 739

Traitement des infections à bacilles pyocyaniques
par des bactériophages adaptés par sélection.

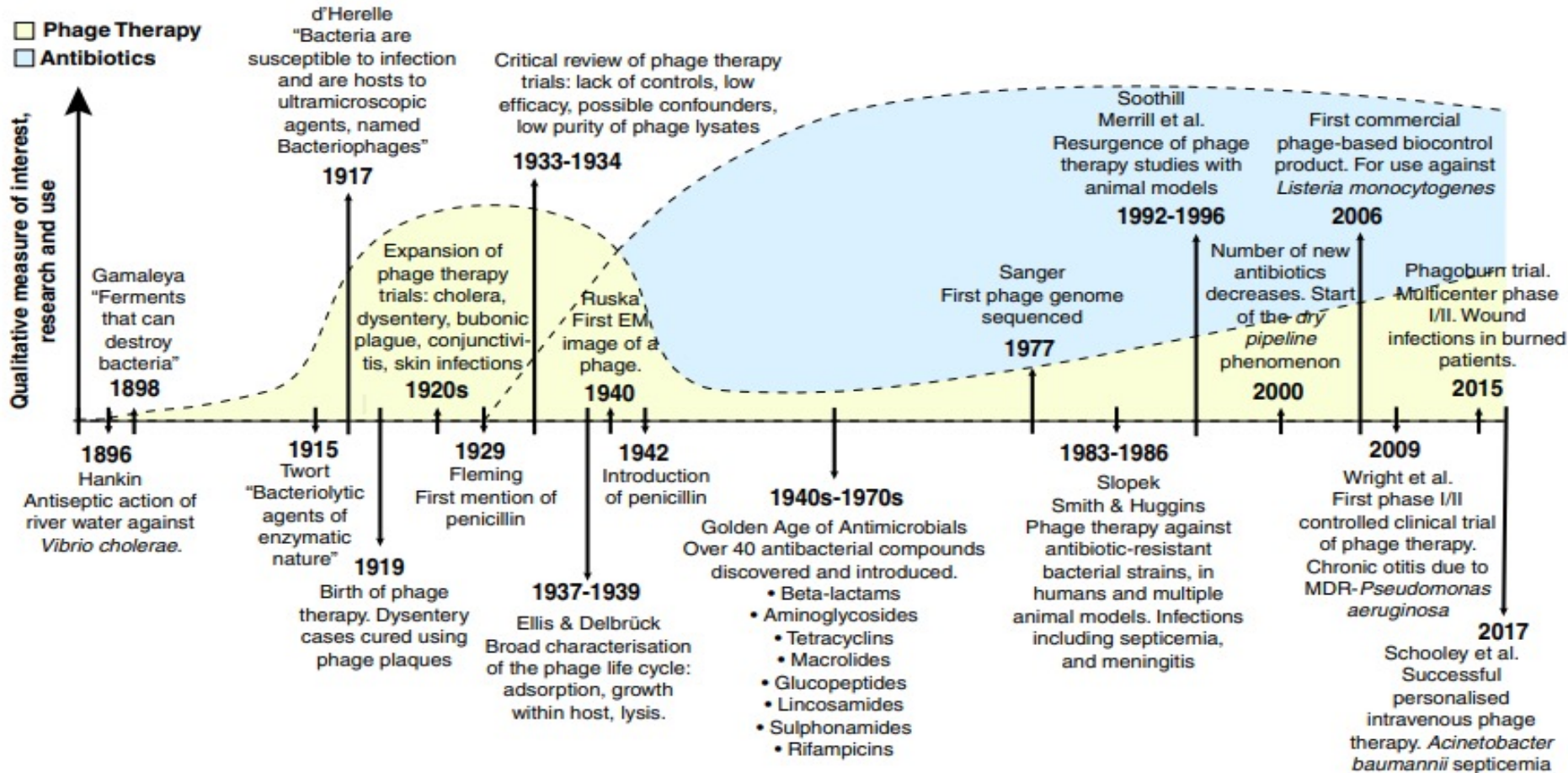
Par MM. André BERTHOYE et A.-L. COURTIEU.

Les bacilles pyocyaniques sont fréquemment résistants aux antibiotiques usuels. Cependant, le nombre des cas d'infections (méningées, cutanées, otitiques, bronchiques, pleurales, fistulaires, etc...) qui peuvent leur être attribués semble être en augmentation. Leur caractère rebelle est une de leurs caractéristiques. Il semblait donc logique de leur opposer une thérapeutique différente de celles classiquement proposées. Depuis longtemps on connaissait l'existence de bactériophages actifs sur le bacille pyocyanique. Mais l'emploi de stock-bactériophages est d'une efficacité très limitée. Par contre, l'adaptation par sélection d'une variété de bactériophage à la souche isolée du malade permet une action beaucoup plus certaine. Si la production sur bouillon nutritif ordinaire suffit pour certains usages par voie externe, il est par contre indispensable de le faire sur un milieu spécial au sérum humain dilué pour pouvoir l'introduire sans danger par toutes les voies (intracrâniennes, intraveineuse, intrapleurale, etc...).

Un certain nombre de cas ainsi traités avec succès sont rapportés dans cette publication.

1959

History

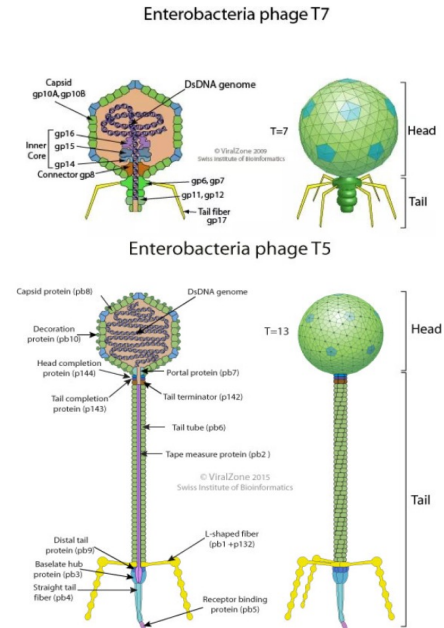


What is a « bacteriophage »?

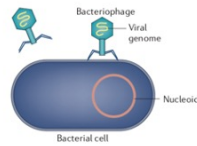
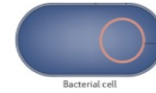
Viral therapy for bacterial infections

⇒ **Each bacteriophage is specific to one bacterium**

⇒ **Not decimating the microbiota**



Phage therapy – Lytic cycle



Phage therapy – Lytic cycle

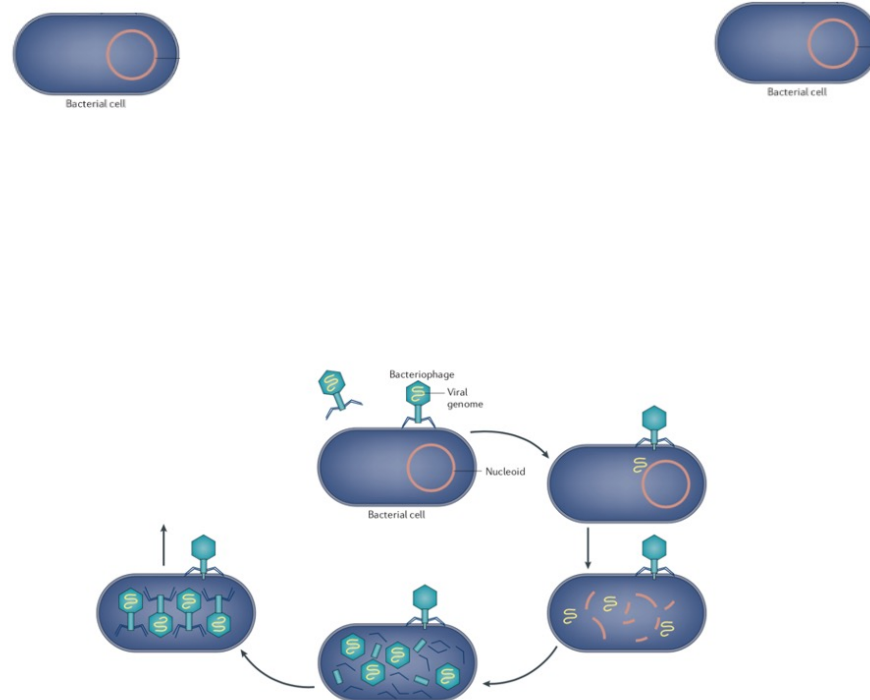


Figure 1 | **The phage life cycle.** The life cycle of bacteriophages involves: attachment to the bacterial cell; injection of viral DNA; disruption of the bacterial genome; synthesis and assembly of new phages; bacterial cell lysis and phage release.

Phage therapy – Lytic cycle

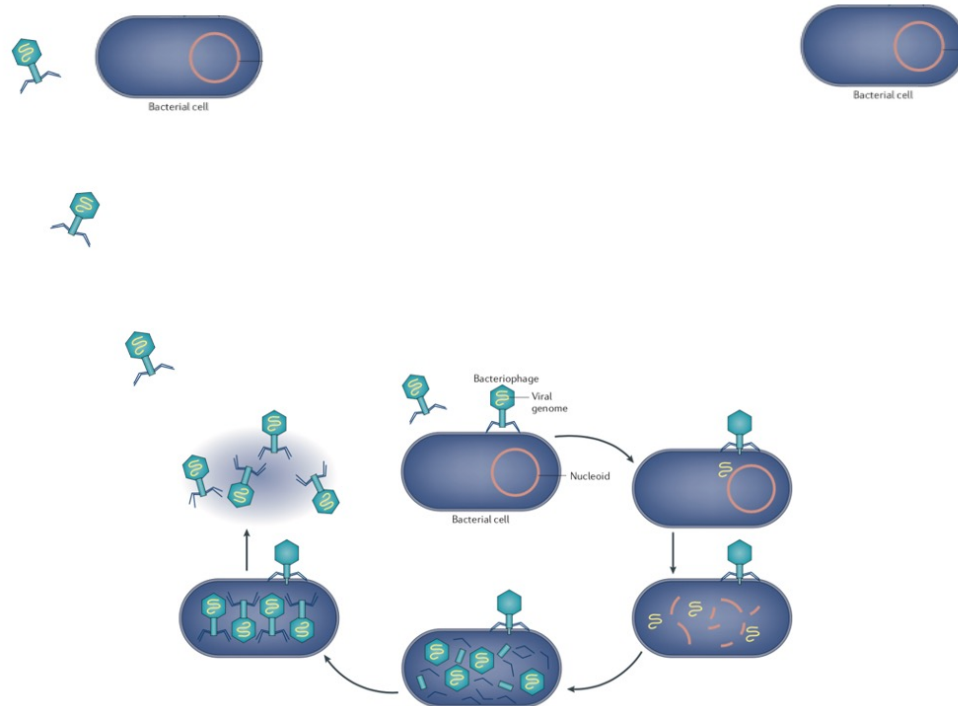


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Phage therapy – Lytic cycle

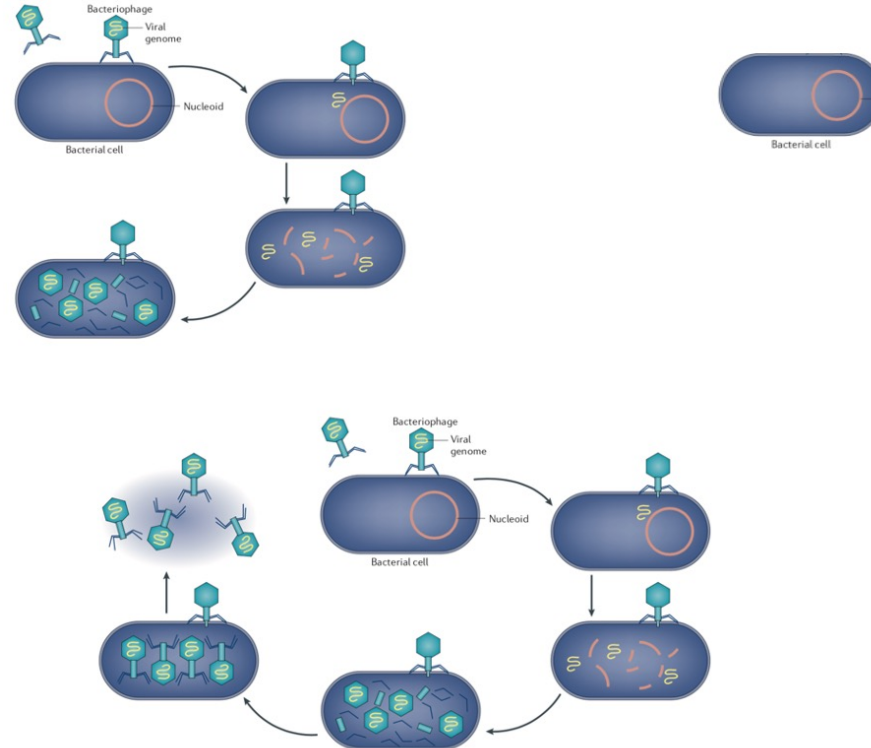


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Phage therapy – Lytic cycle

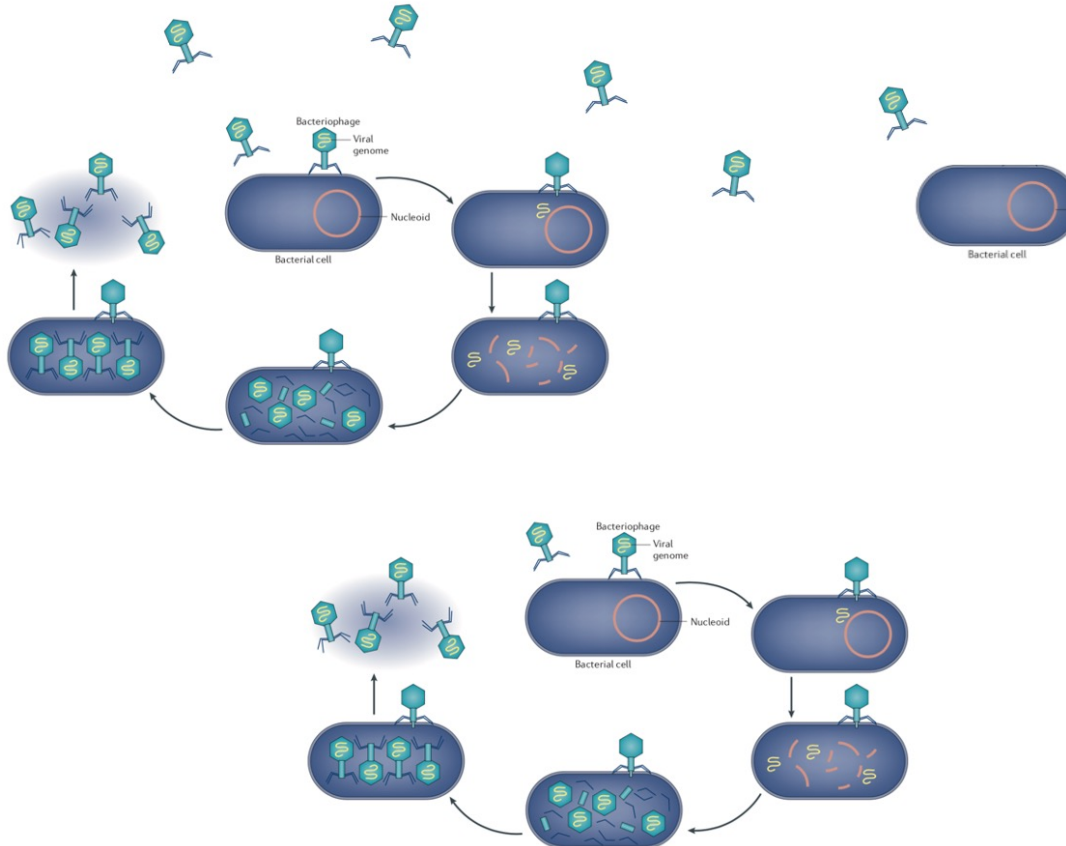


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Phage therapy – Lytic cycle

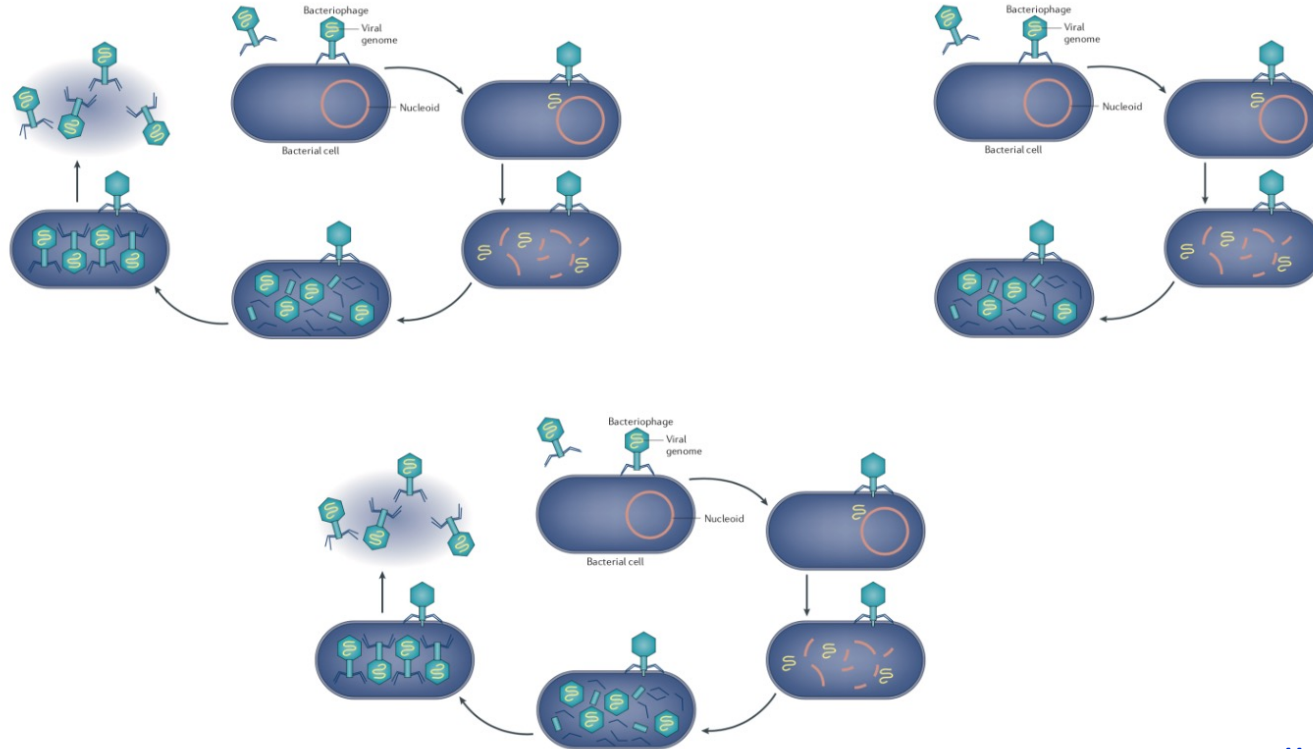


Figure 1 | **The phage life cycle.** The life cycle of bacteriophages involves: attachment to the bacterial cell; injection of viral DNA; disruption of the bacterial genome; synthesis and assembly of new phages; bacterial cell lysis and phage release.

Phage therapy – Lytic cycle

In theory :

Disappearance of the bacterial community

Disappearance of bacteriophages

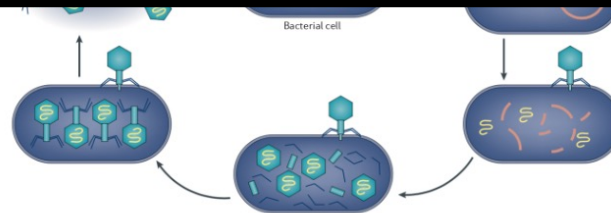
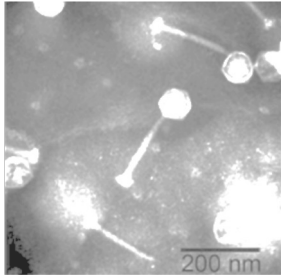


Figure 1 | **The phage life cycle.** The life cycle of bacteriophages involves: attachment to the bacterial cell; injection of viral DNA; disruption of the bacterial genome; synthesis and assembly of new phages; bacterial cell lysis and phage release.

lytic phages have to be used

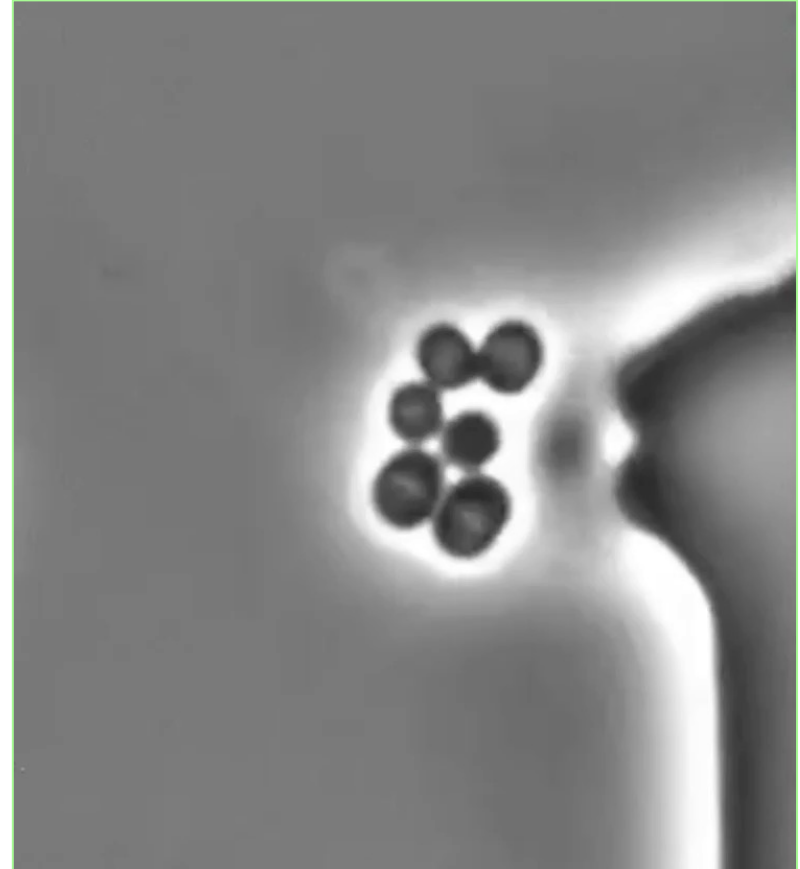
***S. aureus* being lysed by the
Sa2 phage**



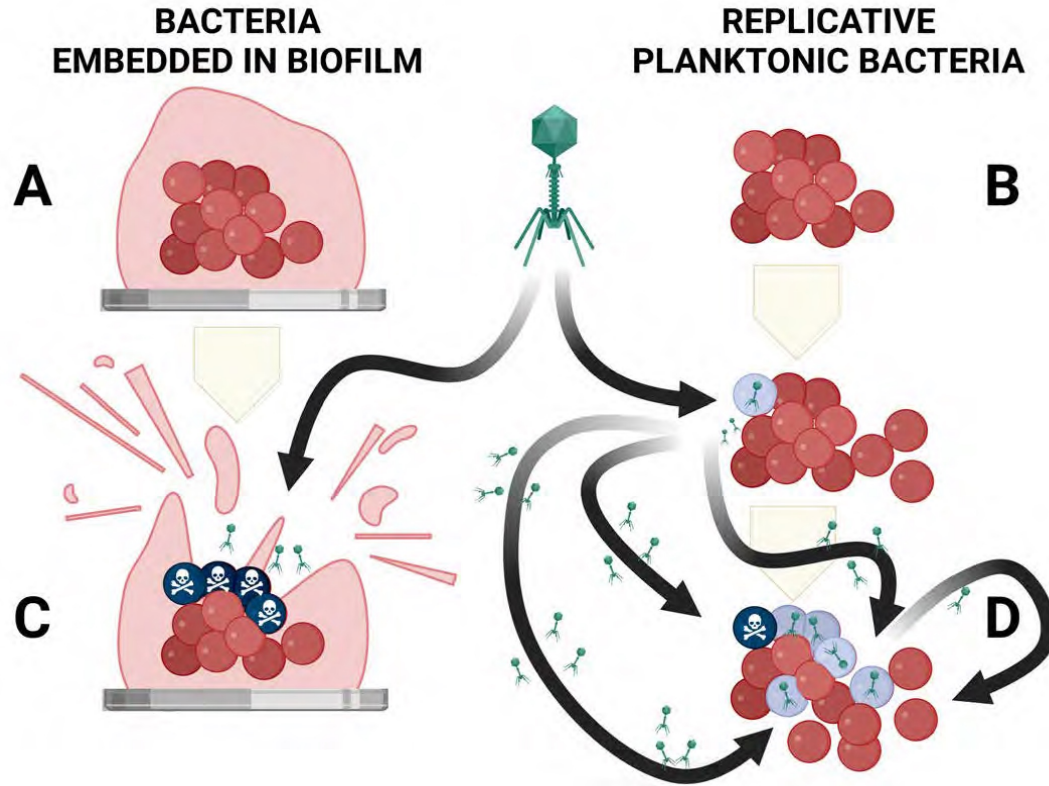
Bacterial DNA appeared in green

Courtesy Pascal Maguin
Luciano Marraffini Lab

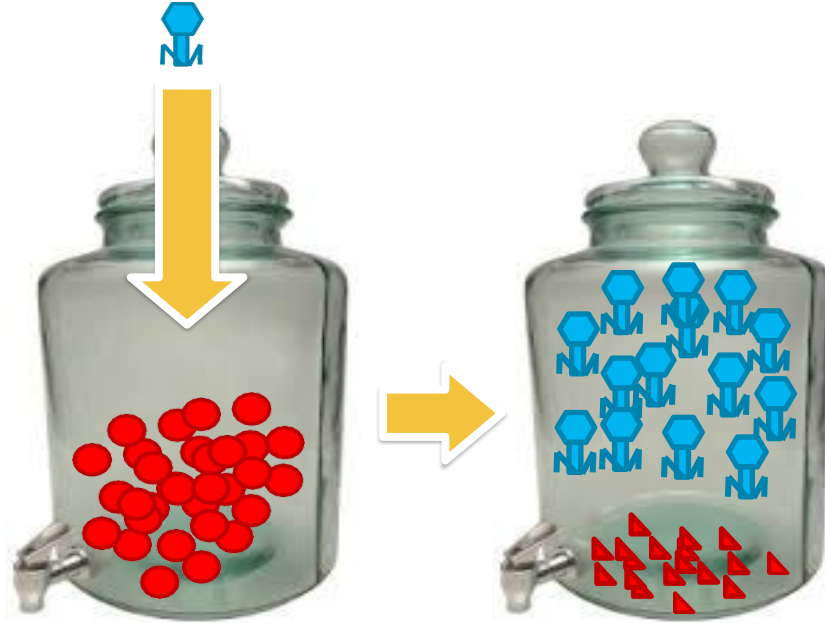
THE ROCKEFELLER UNIVERSITY



Antibiofilm activity



Quality of the bacteriophages cocktail



GMP: Good Manufacturing Practice
with specific purification process

Non GMP



10^6 phages/mL

 **PHERECYDES
PHARMA**

GMP



10^{10} phages/mL

Which bacteria?



S. aureus ✓

S. epidermidis ✗

S. haemolyticus ✗

S. caprae ✗

S. ... ✗

Staphylococcus

Enterobacteria



P. aeruginosa ✓

P. putida ✗

Acinetobacter spp. ✗

Stenotrophomonas spp. ✗

...

Non-fermenting

Mycobacteria

M. tuberculosis ✗

M. abscessus ✗

M. avium ✗

...

E. Coli ✗

Klebsiella spp. ✗

Proteus spp. ✗

Enterobacter spp. ✗

...

Anaerobics ... ✗

Streptococcus

S. pneumonia ✗

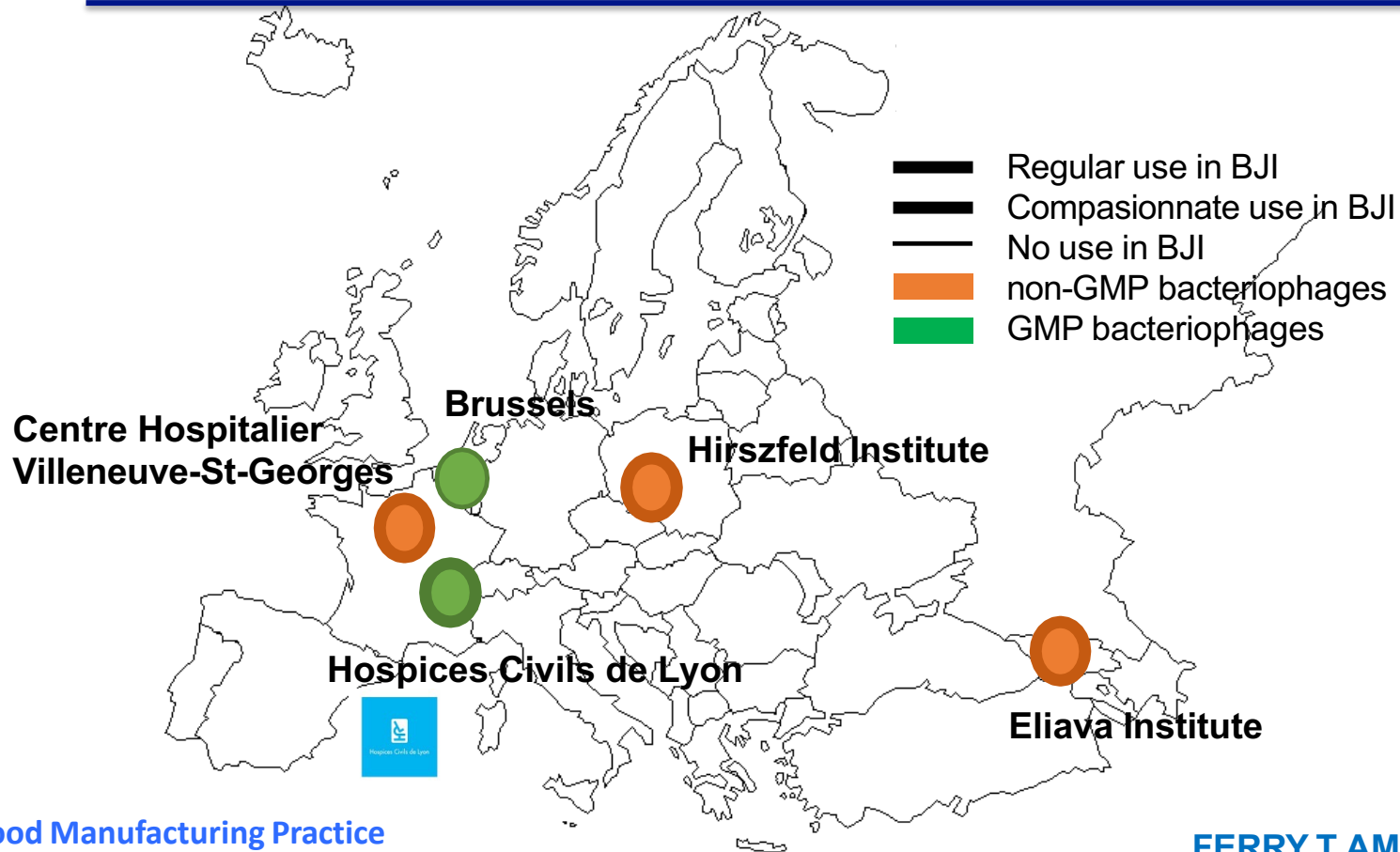
S. pyogenes ✗

S. mitis ✗

S. oralis ✗

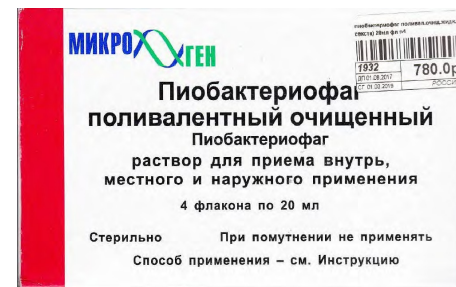
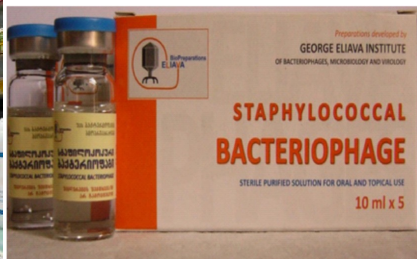
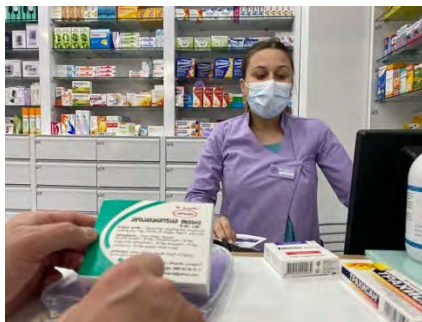
...

Current state - Europe



Current state - Europe

Cocktails produced by the Eliava Institute (GEORGIA)



Professor Andrzej Górski



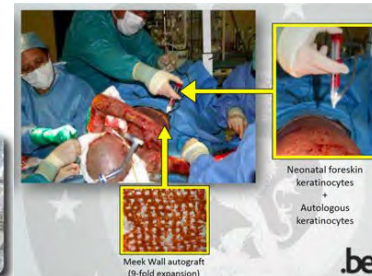
Communication

Processing Phage Therapy Requests in a Brussels Military Hospital: Lessons Identified

Sarah Djebara ^{1,*}, Christiane Maussen ¹, Daniel De Vos ², Maya Merabishvili ², Benjamin Damanet ¹, Kim Win Pang ¹, Peggy De Leenheer ¹, Isabella Strachinaru ¹, Patrick Soentjens ¹ and Jean-Paul Pimay ²



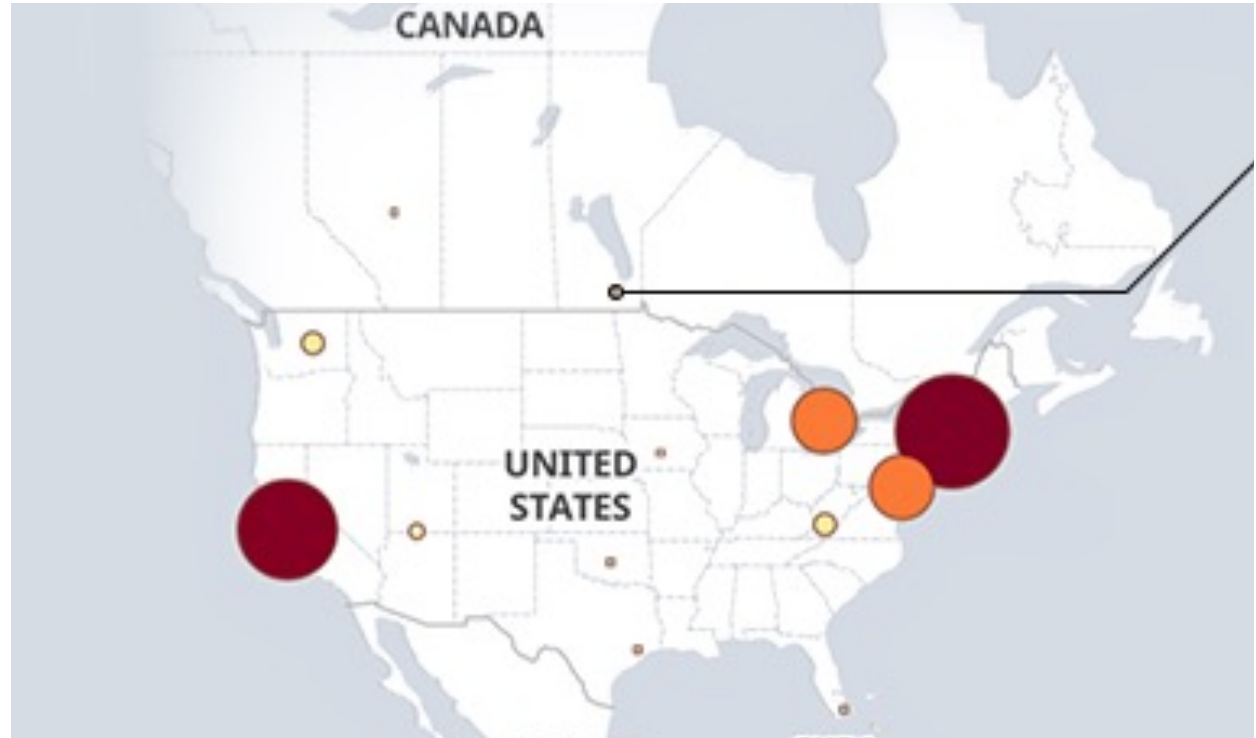
Reine Astrid Hospital



Current state - USA



Tailored Antimicrobials and Innovative
Laboratories for Phage (Φ) Research



Emerging bacteriophages solutions in USA

Current state - China



Current state - China

Shanghai, the origin of phage therapy in China



Emerging Microbes & Infections
2021, VOL. 10
<https://doi.org/10.1080/22221751.2021.1902754>



Pre-optimized phage therapy on secondary *Acinetobacter baumannii* infection in four critical COVID-19 patients

Nannan Wu^{②†}, Jia Dai[†], Mingquan Guo^{②,4†}, Jianhui Li[†], Xin Zhou^{②†}, Feng Li⁵, Yuan Gao⁵, Hongping Qu⁶, Hongzhou Lu^⑥, Jing Jin⁹, Tao Li⁹, Lei Shi¹, Qingguo Wu⁵, Ruoming Tan⁶, Mingli Zhu⁴, Lan Yang⁵, Yun Ling¹, Shunpeng Xing⁴, Jianzhong Zhang¹, Bangxin Yao⁵, Shuai Le^{④,1}, Jingmin Gu^{④,11}, Jinzhong Qin^{②,9,1}, Jie Li⁹, Mengjun Cheng⁴, Demeng Tan⁶, Linlin Li⁹, Yiyuan Zhang⁴, Zhaoqin Zhu⁹, Jinfeng Cai⁹, Zhigang Song⁹, Xiaokui Guo^{②,9}, Li-Kuang Chen^{②,4,9} and Tongyu Zhu^{②,4,9}

On March 24, 2023, “Chongqing Phage Clinical Application Technology Center”



Phage cleaner products

=> 2017 Taiwan Innovation Award



Courtesy of ShengDong YANG

Bone and joint infections

Post-trauma
long-bone
osteomyelitis



Surgery
(debridement & reconstruction)
Antibiotics

Chronic
prosthetic-joint
infection



Surgery
(prosthesis explantation)
Antibiotics

Spinal infection
with abscess and
bone destruction



Surgery
(debridement & stabilization)
Antibiotics

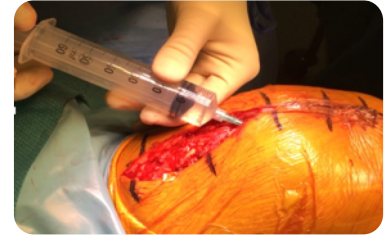
Which indications?

- Complex bone infection with or without implant
- No mechanical problem in the foreground
- Salvage procedure



Which procedures? CONSERVATIVE ++

- Intravenous
- Local injection under ultrasound
- Local injection after DAIR by arthroscopy
- Local injection after DAIR by arthrotomy

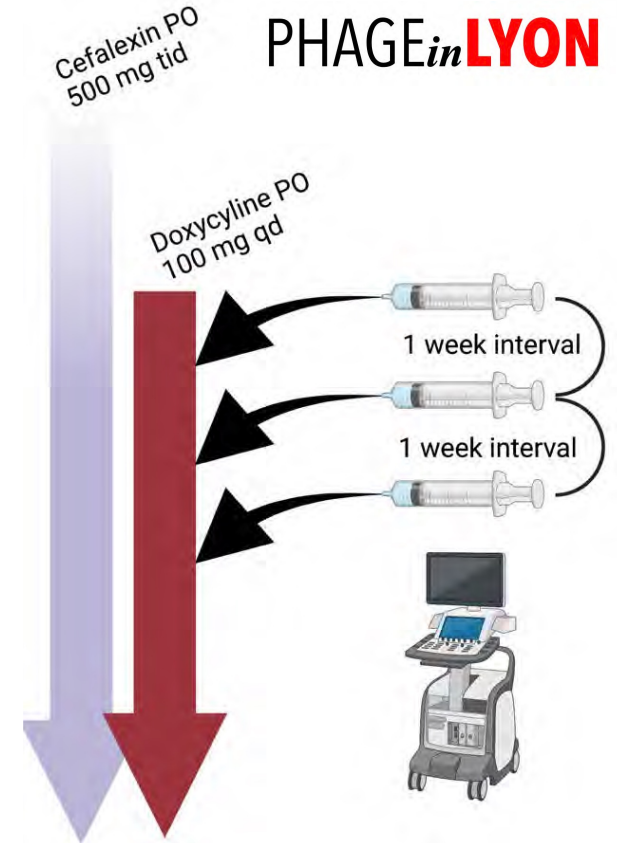


+/- flap



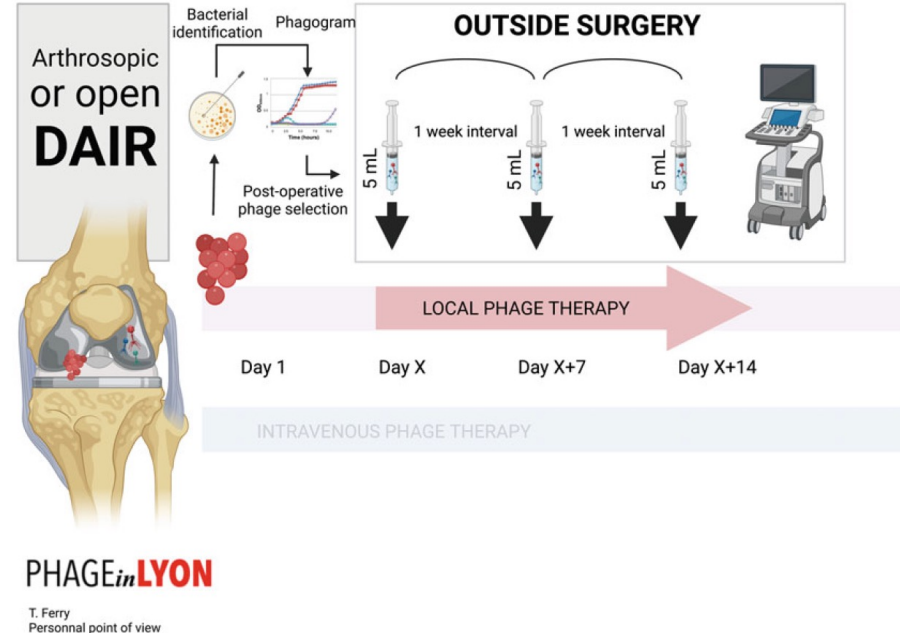
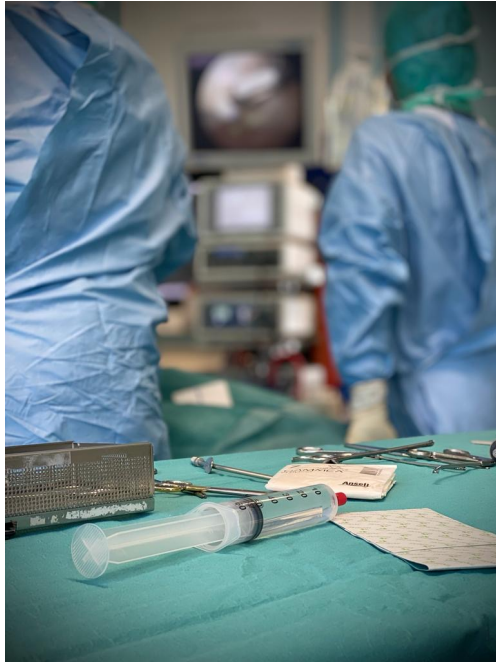
Which procedures?

- Local injection under ultrasound



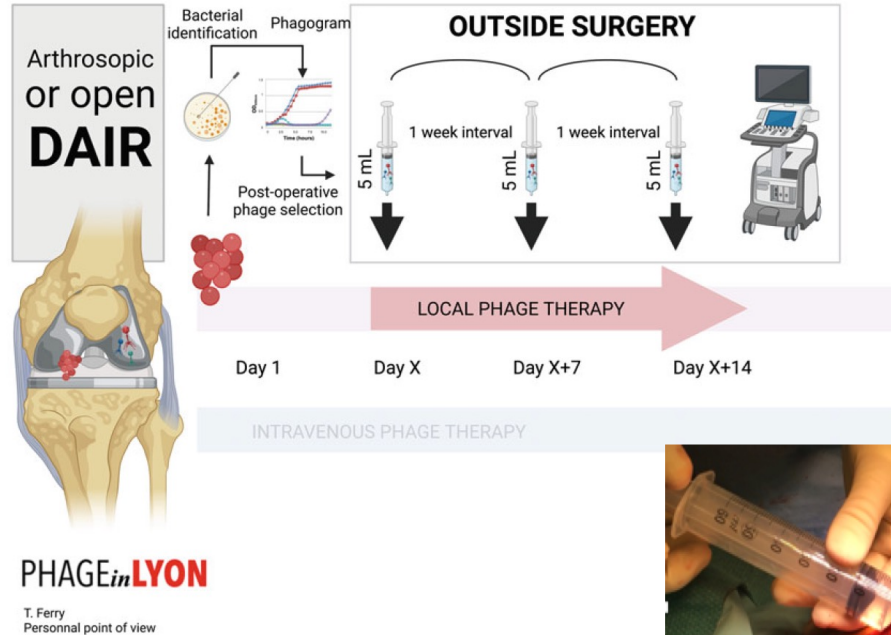
Which procedures?

- Local injection after DAIR by arthroscopy



Which procedures?

- Local injection after DAIR by arthrotomy



Combination of several therapies

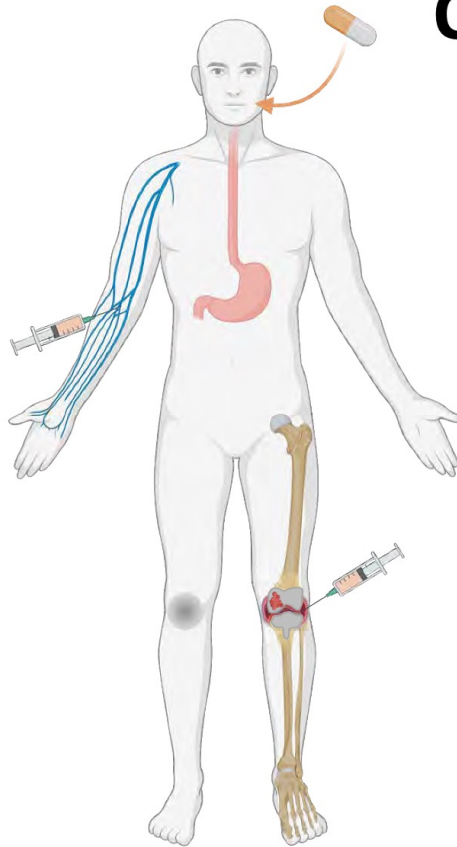
Oral antibiotics

Local therapy
Surgery

No surgery
Arthroscopic DAIR
Open DAIR (SoC)
Prosthesis exchange (SoC)

Local phages

IV antibiotics
IV phages

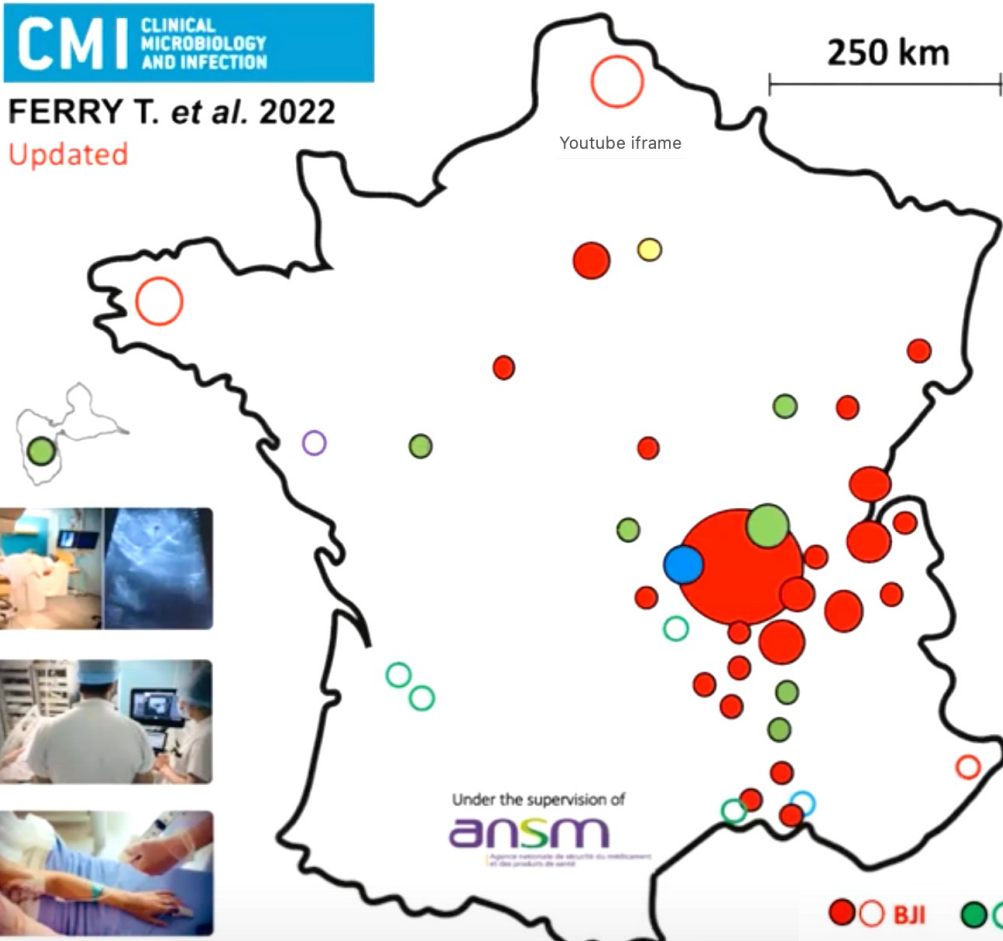


Implementation of a Phage Therapy Center in a CRIOAc

CMI CLINICAL
MICROBIOLOGY
AND INFECTION

FERRY T. et al. 2022

Updated



PHAGE*in***LYON**



59 patients in Lyon since 2017

75% of of whole treated patients in France



- 55 with phages from
- 4 with phages from



PHERECYDES
PHARMA



- 46 **BJI** (inclusion 38 **PJI**)
- 10 **endocarditis/vascular graft**
- 3 **lung infections** (VAP + bacteremia, pneumonia in lung graft bronchiectasia, cystic fibrosis exacerbation)

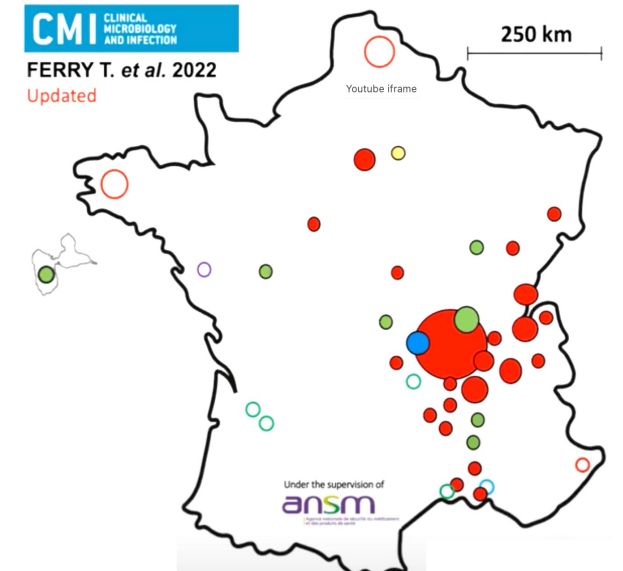
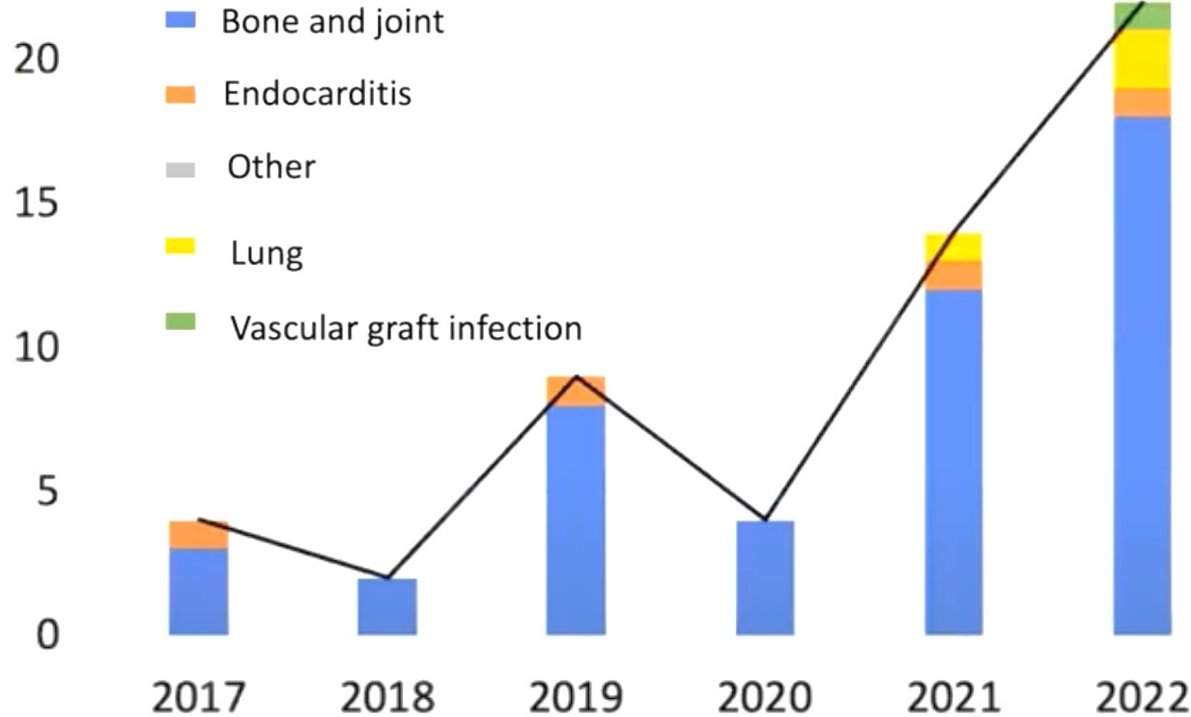


+ 14 patients managed outside Lyon

including 1 patient in Sweden and 1 in Switzerland



Phage Therapy in Lyon CRIOAc

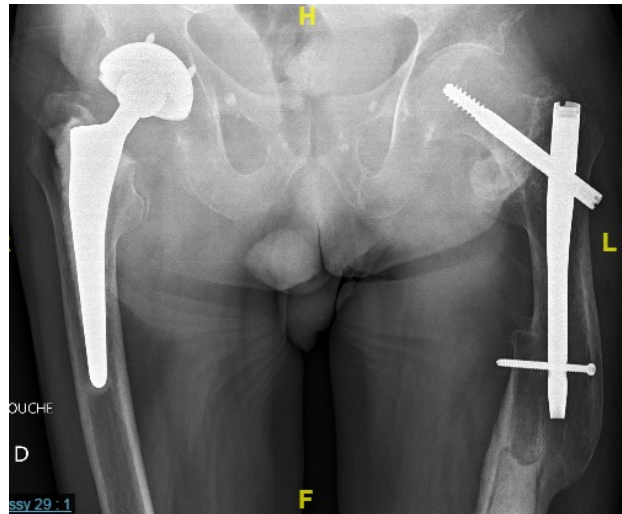


Source: T. Ferry

●○ BJI ●○ Endocarditis ●○ Pneumonia ●○ Burn ●○ Abscess

Clinical Case: To avoid Amputation

- 80-year-old man
- Relapsing right knee PJI (*S. aureus*)
- Failure under suppressive oral therapy
- Candidate for amputation



Clinical Case: To avoid Amputation



Phagogram

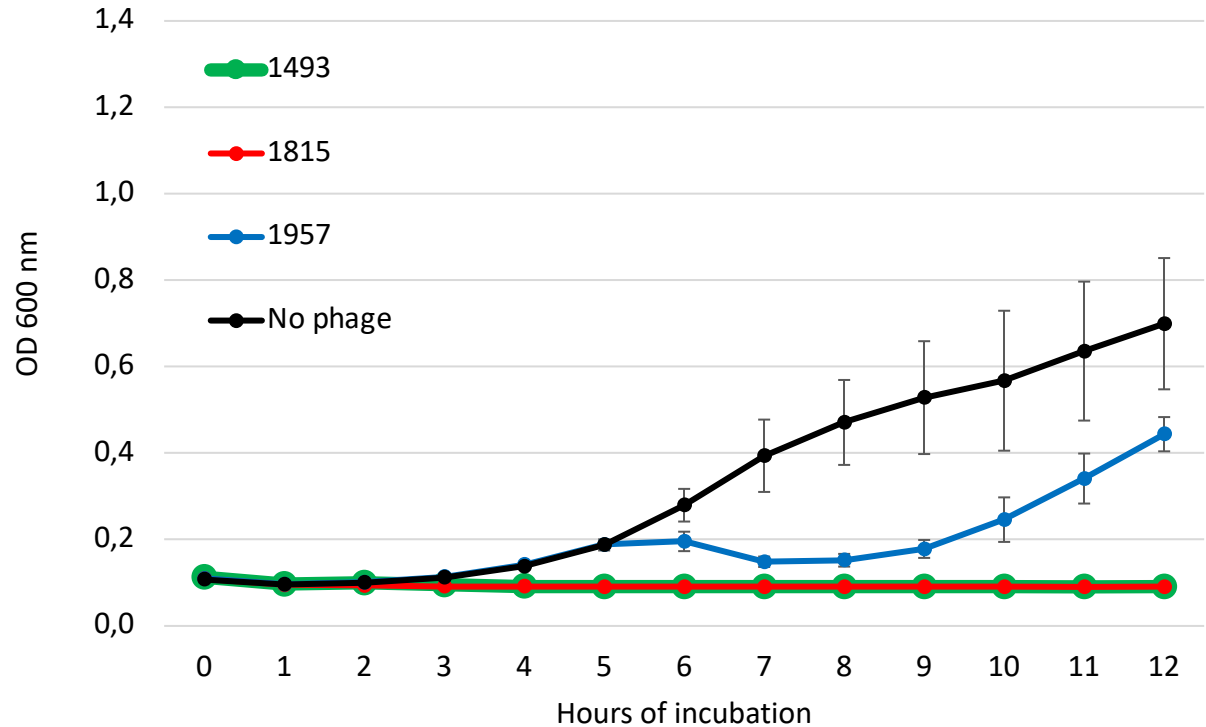


Figure: Determination of the killing activity of 1493, 1815 and 1957 at high MOI against the *S. aureus* patient's strain. Optical density was measured at 600 nm to quantify cell density of the culture. The bacterial concentration over time of the strain without phage is indicated in black. The bacterial concentration over time of the patient's strain in the presence of phages 1493, 1815 and 1957 at the highest MOI is indicated in green, red and blue, respectively.

Clinical Case: To avoid Amputation



PHERECYDES
PHARMA

Anti-*S. aureus* Bacteriophages



1 mL

Phage A



1 mL

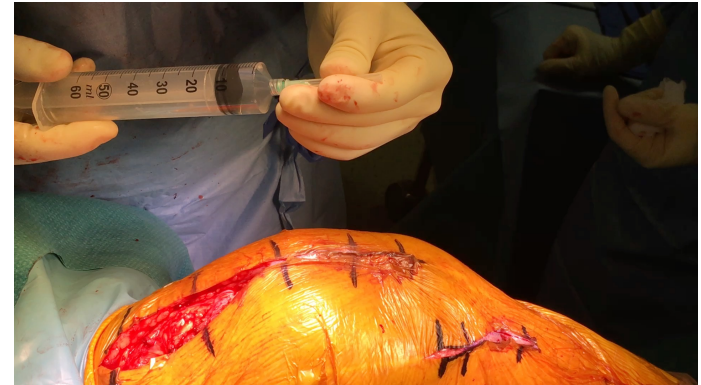
Phage B



1 mL

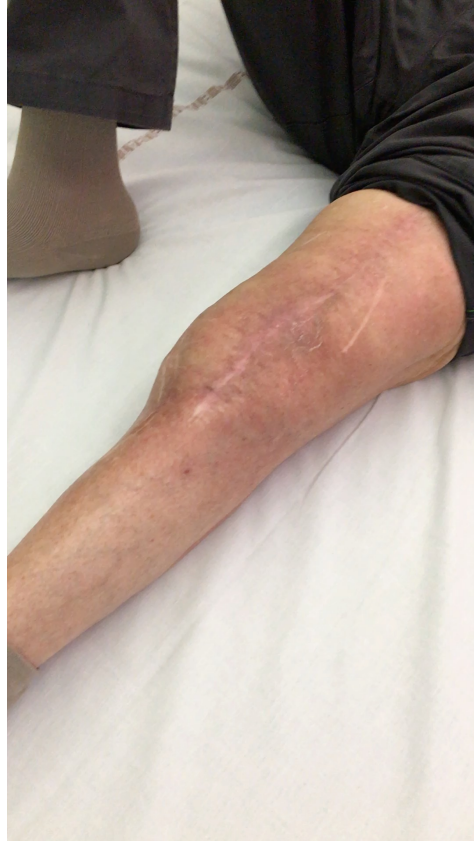
Phage C

Hospital pharmacy



Hospices Civils de Lyon

Clinical Case: To avoid Amputation



At the last follow-up
(>3 years) with
suppressive antibiotic

“The bacteriophages saved my life, he insists.
I never thought one day to walk again. And to
say that doctors were talking about cutting
my leg off!” R.N.

Clinical Case: Phage with DAC gel

- 52-year-old man
- **Severe trauma with left femur fracture**
- **Left arm palsy**
- **Implantation of large tumoral left knee prosthesis**
- **2-stage exchange** (multidrug resistant *S. epidermidis* infection)
- **Relapse 2 years later** (*S. aureus* in a collection)
- Transfemoral amputation was proposed

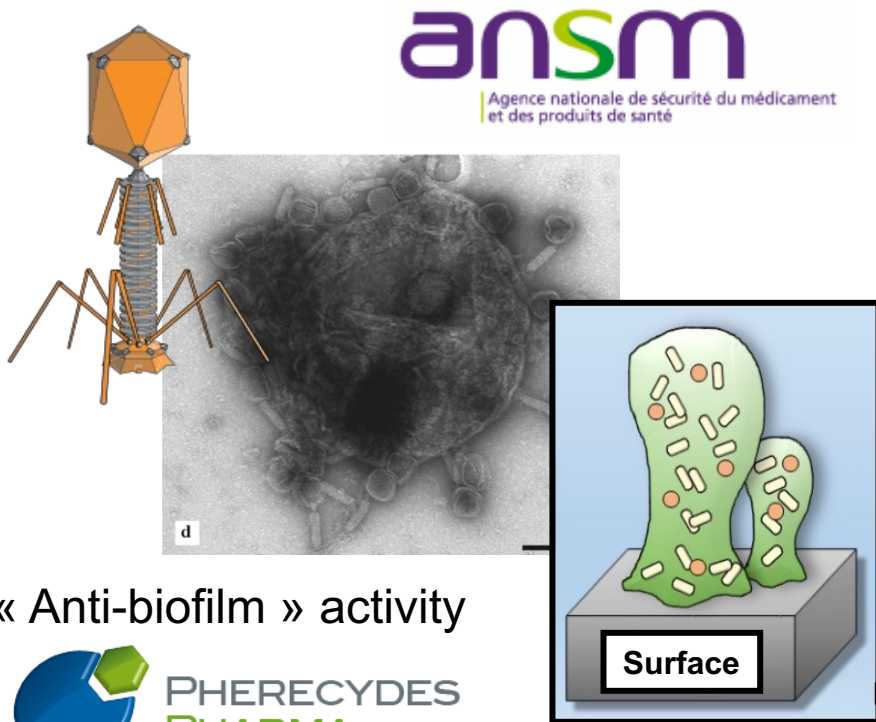


Clinical Case: Phage with DAC gel

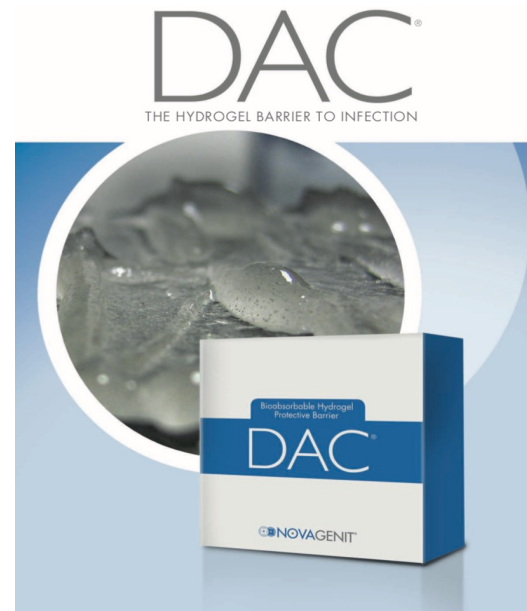


Clinical Case: Phage with DAC gel

‘DAIR’+ SKIN AND SOFT TISSUE FLAP + antibiotics

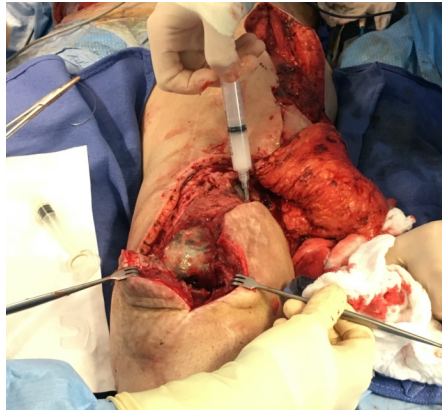
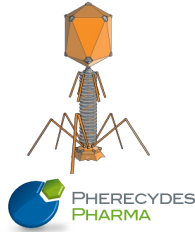


+



Bacteriophages carrier
Prevention of surinfection

Clinical Case: Phage with DAC gel



Clinical Case: Phages by US

62 years old

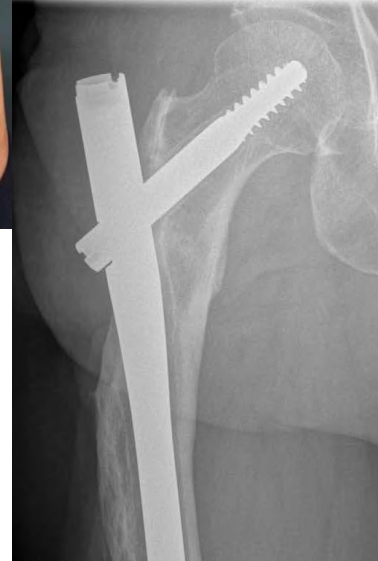
Sarcoma of the thigh

=> Radiotherapy

Fracture => Femoral nail

Recurrent infections

S. aureus

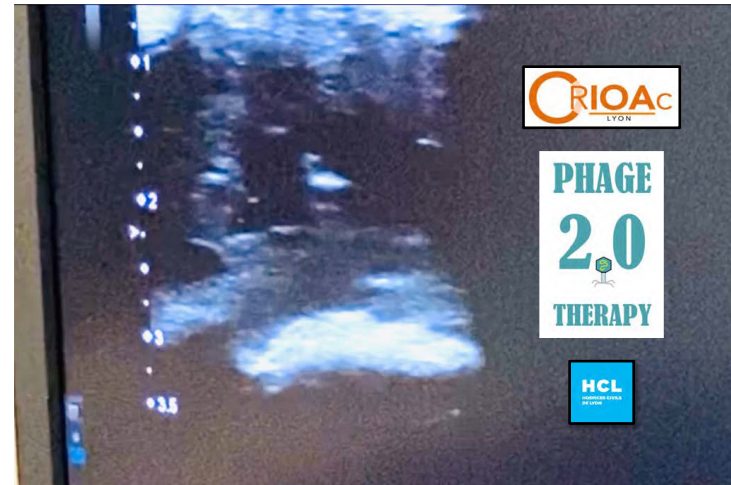


Clinical Case: Phages by US

No surgery

Personalized phage cocktail

One injection: Highly purified phage cocktail 10^9 phages/mL



Clinical Case: Phages by US

Suppressive antibiotic

At 4 years: good outcomes



Clinical Case: Phages because medical contraindication

frontiers
in Medicine
2021

88-year-old man

Relapsing *P. aeruginosa*
prosthetic left knee infection

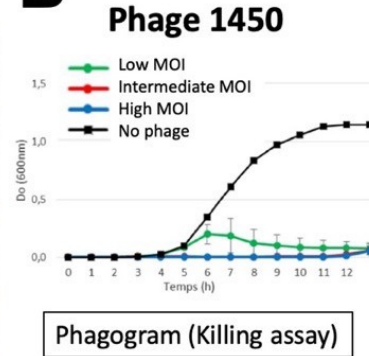
End stage cardiac failure

Contraindicated to open DAIR

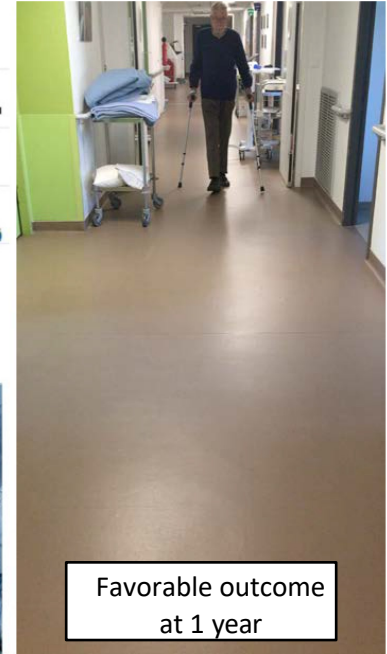
A



B



D





**Favorable outcome
at 1 year**





**Favorable outcome
at 1 year**



BUT...

Not always possible

Clinical case Mr R. (untreated)

45 years old

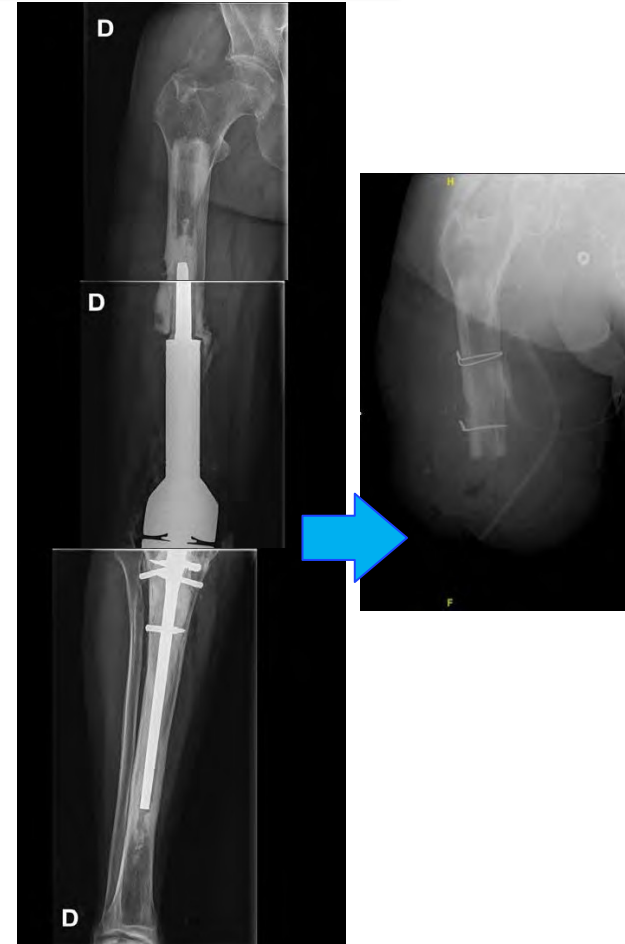
Bone resection for a sarcoma

Tumoral prosthesis

Recurrent infection

S. aureus: PHAGORESISTANT

E. coli : NO PHAGE is available



High cost

Very Expensive

100 000 € to treat a patient (one time)



⇒ **Compassionate treatment** in Reference center after multidisciplinary consultation meeting

⇒ **Inclusion in Clinical Studies** (PhagoDAIR)

Which data for phages?

16 papers:

- 15 case reports
- 1 clinic research
- 42 patients
- Most common pathogen : *Staphylococcus aureus*

Table 1. Basic information of clinical studies on bacteriophage in PJI

No.	Author	Year	Country	Number of PJI patients	Patient's Information						Bacteria	Co-morbidities
					Gender	Age	Numbers of the surgery	Prosthetic joint	Date of the surgery			
1	Ferry et al.[18]	2018	France	1	Female	80	6	Right Hip	2017		Multidrug-resistant <i>Pseudomonas aeruginosa</i> and Methicillin-susceptible <i>Staphylococcus aureus</i> (fully susceptible except <i>Staphylococcus aureus</i> from the site of infection. The resistance	diabetes mellitus type 2 and mild chronic kidney injury.
2	Patey et al.[19]	2018	F									
3	Tkhilashvili et al.[20]	2019	Ge									
4	Doub et al.[21]	2020										
5	Ferry et al.[22]	2020	France	3	Male	80	2	Left Knee	2015		Methicillin-susceptible <i>Staphylococcus aureus</i> , MSSA	parkinson disease, cardiac
6	Ferry et al.[23]	2020	F									
7	Cano et al.[24]	2021										
8	Doub et al.[25]	2021										
9	Ferry et al.[26]	2021	F									
10	Neuts et al.[27]	2021	Net									
11	Ramirez-Sanchez et al.[28]	2021										
12	Schoeffel et al.[29]	2022										
13	Racenis et al.[30]	2022	L									
14	Cesta et al.[31]	2023										
15	Fedorov et al.[32]	2023	F									
16	Doub et al.[33]	2023	USA	1	Male	69	> 3	Left Knee	NR		<i>Staphylococcus aureus</i> , MSSA: 8 <i>Staphylococcus aureus</i> , MRSA: 1 <i>Enterococcus faecalis</i>	atrial fibrillation, diabetes and hypertension

Clinical Infectious Diseases

SUPPLEMENT ARTICLE



Phage Therapy as a Novel Therapeutic for the Treatment of Bone and Joint Infections

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REVIEW



Bacteriophage therapy as an innovative strategy for the treatment of Periprosthetic Joint Infection: a systematic review

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Conclusion

- **Promising for Complex PJI**
=> Salvage procedure
- **Well described process**
- **But it is not relevant for all bacterial infections**
- **Expensive - Few scientific data currently - In progress**



Lyon - FRANCE



Thank you

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