Fagoterapia en el tratamiento de las infecciones causadas por *Staphylococcus aureus* ¿qué evidencia tenemos?

Phage therapy in the treatment of infections caused by *Staphylococcus aureus* what evidence do we have?

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Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS UMR5308, ENS de Lyon, UCBL1, Lyon, France

Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)









e ational cherche ectiologie

HCL HOSPICES CIVILS DE LYON

What is a « bacteriophage » ?

- Suffix –phage, phagos φαγεῖν (phagein), "to eat", "to devour"
- Viruses that infect ONLY bacteria
- Classification (myoviridae, podoviridae, etc...)
- <u>A phage is specific to A type of bacteria</u>
- 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.









Bacteriophage Distributions and Temporal Variability in the Ocean's Interior



2017

Elaine Luo, Frank O. Aylward,* Daniel R. Mende, OEdward F. DeLong

Daniel K. Inouye Center for Microbial Oceanography: Research and Education, University of Hawaii, Honolulu, Hawaii, USA



Viro 'sphère'

















Ferry T. et al. 2020;24(1):49-56



Lysogenic cycle

Bacterial genetic remodeling







A clear antibacterial activity!

S. aureus being lysed by the Sa2 phage



Bacterial DNA appeared in green

Courtesy Pascal Maguin Luciano Marraffini Lab THE ROCKEFELLER UNIVERSITY



10 to 100 fold smaller than a bacteria

Translucent tap water



X million of ≠ Bactériophage<u>S</u> !!! (targeting environmental bacteria)

 Pharmaceutical preparation

PHAGE*in***LYON**

10⁸ of THREE <u>LYTIC</u> bacteriophages/mL (targeting *S. aureus*)







History of phage therapy

- Felix d'Herelle (early XXth century)
- Institut Pasteur, Paris







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- He treated <u>shigellosis</u> (diarrhea) in children with <u>oral intake</u> of specific "filtered" <u>bacteriophages</u> that he found in stools of patients who spontaneously healed from... shigellosis







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- He founded the <u>"Laboratoire Français</u> des Bactériophages" in Paris and the Eliava institute in Georgia

Eliava Institute (Georgia)





We offer highly. specialized treatments





Cocktails produced in 2021 by the Eliava Institute



- PYO Bacteriophage
- FERSIS Bacteriophage
- STAPHYLOCOCCAL Bacteriophage
- SES Bacteriophage
- INTESTI Bacteriophage
- ENKO Bacteriophage



Bacteriophage ISP (*Myoviridae*)



Merabishvili et al. PloS ONE 2009

T. Ferry. The story of Phage therapy

Not meeting Good Manufacturing Practices (GMP)







10⁶ phages/mL

Clinical case #1

54-year-old man <u>Trauma</u> with open fracture

Post-trauma tibial *S. aureus*

Surgical debridement

Antibiotics

Failure

Management in Georgia for receiving **phage therapy** bacteriophages 10 years ago

Failure



Clinical case #1

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Post-trauma tibial *S. aureus*

Surgical debridement Antibiotics

Failure

Management in Georgia for receiving **phage therapy** bacteriophages 10 years ago

Failure



Clinical case #1		
54-yea Traum	Partial bone necrosis requiring <u>surgery</u>	
Post-trau osteomy	Skin and soft tissue damage requiring surgical coverage	
Surgio Antibio Failure Manag receiv bacter opt	AJOR BIOLOGICAL LIMIT: Bacteriophages have not the ability to: perform bone debridement egenerate skin and soft tissue	

Personalized medicine for BJI

OPTIMAL VS. TARGETED AND SEPTIC ON OPTIMAL OPTIMAL ANTIMICROBIAL THERAPY

PRO





Centre de Ressources Biologiques

UB

Centre de Référence des Infections Ostéo-Articulaires complexes



Réseau des CRIOAc Mandat 2017-2022

le-Tourcoing **STAPHYLOCOOUES** Marine ntre National de Référence Rem Strasbourg Pr. Tristan Ferry Pr. Sébastien Lustig MD. PhD MD, PhD **Multidisciplinar management of** Orthopaedic surgeon Infectiologist the patient Lvon Better understanding of the Pr. Frédéric Laurent PharmD, PhD pathophysiology of BJI Microbiologist 🖐 Inserm

HOSPICES CIVILS

DE LYON

Centre nternational

de Recherche

en Infectiologie

Promotion of innovative treatments

Medical innovations to maintain the function in patients with chronic PJI for whom explantation is not desirable: a pathophysiology-, multidisciplinary-, and experience-based approach





Centre de Référence des Infections Ostéo-Articulaires complexes

Brussels

Pelgium

Ger



Living place of patients who are managed in Lyon





Personalized medicine for BJI

OPTIMAL VS. TARGETED AND SEPTIC ON OPTIMAL OPTIMAL ANTIMICROBIAL THERAPY

PRO

Personalized medicin

Antibiotic<u>S</u>-loaded PMMA cements

Antibiotic-loaded bone substitutes

ADJUVANT INNOVATIVE ANTI-INFECTIVE AGENTS

PRO

Bacteriophages

Bacteriophagederived lysins

New antibiotics targeting the biofilm

OPTIMAL VS. TARGETED AND SEPTIC ON OPTIMAL OPTIMAL ANTIMICROBIAL THERAPY

Not meeting Good Manufacturing Practices (GMP)



T. Ferry. The story of Phage therapy



A clear antibacterial activity! Phage Phagogram **10**¹⁰

10⁸

10⁷

10⁶

10⁵

S. aureus culture on a gelosis



Persisters in chronic BJI

"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"



Persisters in chronic BJI

"Bacterial cells that escape the effects of antibiotics without undergoing genetic change"



Persisters in chronic BJI "Bacterial cells that escape the effects of antibiotics without undergoing genetic change" **Bacteriophages** have anti-persister activity aureus Osteoblast Osteoclas Osteocy implan/



C. Kolenda et al. Antimicrob Agents Chemother 2019



Centre International de Recherche RIOA C Lyon 1

vancomycin













HOSPICES CIVIL

Declaration of Helsinki



Medical Research Involving Human Subjects VVMA ASSOCIATION

Special Communication

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects



worid

MEDICAL

World Medical Association

Unproven Interventions in Clinical Practice

37. I Hospices Civils de Lyon Ethics committee:
 do not "The opinion of the Ethics Committee is that, since there is no effective treatment, therapy is ethically justified. Refraining from therapy in this particular context could be considered as malpractice"

hope of <u>saving life</u>, <u>re-establishing health</u> or alleviating suffering.

In France: compassionate use,

magistral preparation by the hospital pharmacist
62-year-old woman

Leiomyosarcoma

Radiotherapy

Fracture

Osteosynthesis, soft tissue flap

Recurrent S. aureus infection

Proximal and distal **abscesses**

















Conservative surgery

"Debridement And Implant Retention" (DAIR)"?

No surgery!

Local injections of personalized bacteriophages in combination with <u>Antibiotics?</u>







Tristan Ferry Lyon University Hospitals @FerryLyon

Personalized phage cocktail

One shot phage injection

Primary then suppressive antimicrobial therapy

Favorable outcome at 10 months





Impossible to achieve the cure But <u>'freezing'</u> the bacterial multiplication is crucial to <u>save time</u> and <u>avoid complications</u>



Phage Therapy as Adjuvant to Conservative Surgery and Antibiotics to Salvage Patients With Relapsing S. aureus Prosthetic Knee Infection

Tristan Ferry^{1,2,3,4*}, Camille Kolenda^{2,3,4,5}, Cécile Batailler^{2,3,6}, Claude-Alexandre Gustave^{2,3,4,5}, Sébastien Lustig^{2,3,6}, Matthieu Malatray^{3,6}, Cindy Fevre⁷, Jérôme Josse^{2,3,4,5}, Charlotte Petitjean⁷, Christian Chidiac^{1,2,3,4}, Gilles Leboucher⁸ and Frédéric Laurent^{2,3,4,5} on behalf of the Lyon BJI Study group

#PhagoDAIR

80-year-old man

<u>Relapsing MSSA</u> prosthetic left knee infection (past revision)

Failure under suppressive antimicrobial therapy

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)







Amputation (but not feasible !) ?

Doing nothing, but poor clinical situation with <u>risk of</u> complication and death

Conservative surgery

"Debridement And Implant Retention" (DAIR) + <u>innovative approach to</u> <u>disrupt biofilm</u>

Suppressive antimicrobial therapy

PRO

VS.

CON











"Debridement And Implant Retention" (DAIR)





"PhagoDAIR"



One shot peroperative phage application after "DAIR"





Post-operative antibiotics:

Daptomycin + Rifampin

<u>At day 4 (only MSSA in all intraoperative samples):</u>

Levofloxacin + Rifampin

<u>Then:</u>

Cefalexin as suppressive antimicrobial therapy







"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.





CASE REPORT published: 16 November 2020 doi: 10.3389/fmed.2020.570572





T. Ferry et al.

CASE REPORT published: 16 November 2020 doi: 10.3389/fmed.2020.570572





T. Ferry et al.

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The Potential Innovative Use of Bacteriophages Within the DAC[®] Hydrogel to Treat Patients With Knee Megaprosthesis Infection Requiring "Debridement Antibiotics and Implant Retention" and Soft Tissue Coverage as Salvage Therapy

Tristan Ferry^{1,2,3,4*}, Cécile Batailler^{2,3,5}, Charlotte Petitjean⁶, Joseph Chateau⁷, Cindy Fevre⁶, Emmanuel Forestier⁸, Sophie Brosset⁷, Gilles Leboucher⁹, Camille Kolenda^{2,3,4,10}, Frédéric Laurent^{2,3,4,10} and Sébastien Lustig^{2,3,5} on behalf of the Lyon BJI Study Group





Arthroscopic <u>"Debridement Antibiotics and Implant</u> <u>Retention"</u> with local injection of personalized phage therapy to salvage a relapsing *Pseudomonas aeruginosa* prosthetic knee infection





Conclusions: The **PhagoDAIR** procedure by **arthroscopy** has the potential to be used **as salvage therapy** for patients with *P. aeruginosa* relapsing PJI, in combination with suppressive antimicrobial therapy. **A Phase II clinical study deserves to be performed to confirm this hypothesis.**

<u>Ultrasound guided local administration</u> of personalized cocktail of bacteriophages followed by suppressive antibiotherapy as salvage therapy in patients with relapsing total femur prosthesis infection



Conclusions: Ultrasound-guided local administration of personalized cocktail of GMP bacteriophages followed by suppressive antibiotherapy in patients with relapsing total femur PJI has the potential to be used as salvage therapy to control the infection and avoid disarticulation. Dramatic superinfection could be diagnosed at the time of phage administration.

<u>Intravenous</u> administration of personalized cocktail of bacteriophages as salvage therapy in combination with ceftazidime/avibactam in patients with relapsing *P. aeruginosa* bacteremia: Lesson learned from two cases



Conclusions: The type of filter used for the magistral preparation and the duration of the perfusion influenced the phage titer, as the titer in the patient's blood. Personalized GMP bacteriophage therapy has the potential to be used as salvage therapy of *P. aeruginosa* intravascular implant infections.



Clinical Infectious Diseases

BRIEF REPORT



Successful Treatment of Antibioticresistant, Poly-microbial Bone Infection With Bacteriophages and Antibiotics Combination Ran Nir-Paz, ¹Daniel Gelman, ²³ Ayman Khouri, ⁴ Brittany M. Sisson, ⁵ Joseph Fackler, ⁵ Sivan Alkalay-Oren, ² Leron Khalifa, ² Amit Rimon, ²³ Ortal Yerushalmy, ² Reem Bader, ¹ Sharon Amit, ¹ Shunit Coppenhagen-Glazer, ² Matthew Henry, ⁶ Javier Quinones, ⁶ Francisco Malagon, ⁶ Biswajit Biswas, ⁶ Allon E. Moses, ¹ Greg Merril, ⁵ Robert T. Schooley, ⁷ Michael J. Brownstein, ⁵ Yoram A. Weil, ⁴ and Ronen Hazan²

¹Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University Medical Center, ²Institute of Dental Sciences, Faculty of Dental Medicine, The Hebrew University, ³Tzameret, The Military Track of Medicine, The Hebrew University-Hadassah Medical School, and ⁴Orthopedic Surgery Department, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; and ⁵Adaptive Phage Therapeutics, Gaithersburg, and ⁶The Geneva Foundation and Biological Defense Research Directorate Naval Medical Research Center, Frederick, Maryland; and ⁷Department of Medicine, Division of Infectious Diseases, University of California San Diego, La Jolla, California





Case Report

Salvage Bacteriophage Therapy for a Chronic MRSA Prosthetic Joint Infection

James B. Doub ^{1,*}, Vincent Y. Ng ², Aaron J. Johnson ², Magdalena Slomka ¹, Joseph Fackler ³, Bri'Anna Horne ³, Michael J. Brownstein ³, Matthew Henry ⁴, Francisco Malagon ⁴ and Biswajit Biswas ⁴

Clinical Infectious Diseases



MDP



Phage Therapy for Limb-threatening Prosthetic Knee *Klebsiella pneumoniae* Infection: Case Report and In Vitro Characterization of Anti-biofilm Activity

Edison J. Cano,¹² Katherine M. Caflisch,²³ Paul L. Bollyky,⁴ Jonas D. Van Belleghem,⁴ Rohin Patel,¹²⁵ Joseph Fackler,⁶ Michael J. Brownstein,⁶ Bri Anna Home,⁶ Biswajit Biswas,⁷ Matthew Henry,²³ Francisco Malagon,⁷ David G. Lewallen,⁸ and Gina A. Suh¹



PHAGE*in*LYON

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Tristan Ferry Lyon University Hospitals @FerryLyon



Today, we treated @CHUdeLyon a 20th patient with ultrasound injection of #bacteriophages for a relapsing prosthetic joint infection due to multidrug-resistant #Pseudomonas aeruginosa! We hypothethize that #phagetherapy can help to control this kind of dramatic infection!



51

17 11

PHAG-one

MINISTÈRE DE L'ENSEIGNEMENT SUPÉRIEUR, DE LA RECHERCHE ET DE L'INNOVATION Liberté Égalité Fraternité



Purified <u>academic</u> phages Usable in the next 5 years





Bacteriophage Lysins

Vincent A Fischetti @microbephage



Tristan Ferry Lyon University Hospitals @FerryLyon

Incredible talk of Pr. Vincent A. Fischetti @microbephage @IDWeek2019 about the great potential of #bacteriophage #lysins to induce bacterial explosion... and disappearance! It's good to hear that he discovered lysins that are active against #multidrugresistant #ESKAPE pathogens! Combination Therapy With Lysin CF-301 and Antibiotic Is Superior to Antibiotic Alone for Treating Methicillin-Resistant *Staphylococcus aureus*–Induced Murine Bacteremia

Raymond Schuch,¹ Han M. Lee,¹ Brent C. Schneider,¹ Karen L. Sauve,¹ Christina Law,¹ Babar K. Khan,¹ Jimmy A. Rotolo,¹ Yuki Horiuchi,¹ Daniel E. Couto,¹ Assaf Raz,² Vincent A. Fischetti,² David B. Huang,¹ Robert C. Nowinski,¹ and Michael Wittekind¹

¹ContraFect Corporation, Yonkers, NY, and ²Department of Bacterial Pathogenesis and Immunology, The Rockefeller University, New York, New York





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Combo

CF-301

VAN

Buffer

Arthroscopic debridement, antibiotic and implant retention (DAIR) with local administration of Exebacase (Lysin CF-301) (LysinDAIR) followed by suppressive tedizolid as salvage therapy in elderly patients for relapsing multidrug-resistant *Staphylococcus epidermidis* prosthetic knee infection







Conclusions: Exebacase has the potential to be used as salvage therapy during arthroscopic DAIR in patients with relapsing MDR **S.** *epidermidis* PKI, to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.

Arthroscopic debridement, antibiotic and implant retention (DAIR) with local administration of Exebacase (Lysin CF-301) (LysinDAIR) followed by suppressive tedizolid as salvage therapy in elderly patients for relapsing multidrug-resistant *Staphylococcus epidermidis* prosthetic knee infection



Conclusions: Exebacase has the potential to be used as salvage therapy during arthroscopic DAIR in patients with relapsing MDR *S. epidermidis* PKI, to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.
Conclusion



- Evidence for *in vitro* activity of lytic phages
- There is a real place for phage therapy to maximize clinical success in complex bacterial infections
- Need to identify <u>relevant clinical indications</u>
- Expertise of referral clinical centers
- Evidence for an added value in particular dead-end clinical situations (PJI)



1,0 E 0,8 8 0,6 0 0,4 0,2 0,0 0 1 2 3 4 5 6 7 8 9 10 11 12 Hours of incubation





• Develop and use **<u>purified</u>** bacteriophages

23 patients treated in 4 years

- Industry / health authority / academic collaborations
- Need for <u>Phage discovery</u>, <u>banking</u>, <u>susceptibility</u>, to personalize the therapy
- Need for national phage therapy center(s)
- <u>Clinical trials</u> have to be performed <u>to demonstrate</u> a potential benefit in less severe patients



HCL









Centre International de Recherche en Infectiologie



SAVE THE DATE!!!

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DIRECTION GÉNÉRALE DE L'OFFRE DE SOINS





Hôpitaux Universitaires de Marseille





http://crioac2021.univ-lyon1.fr 5^{ème} Congrès national des CRIOAc À Lyon Les 21-22 octobre 2021 !

Full digital with some sessions in english

Lyon BJI Study group

Coordinator: Tristan Ferry

Infectious Diseases Specialists – Tristan Ferry, Florent Valour, Thomas Perpoint, Florence Ader, Sandrine Roux, Claire Triffault-Filit, Agathe Becker, Anne Conrad, Marielle Perry, Cécile Pouderoux, Nicolas Benech, Pierre Chauvelot, Johanna Lippman, Evelyne Braun, Christian Chidiac

Surgeons – **Sébastien Lustig**, Elvire Servien, Cécile Batailler, Stanislas Gunst, Axel Schimdt, Matthieu Malatray, Elliot Sappey-Marinier, Michel-Henry Fessy, Anthony Viste, Jean-Luc Besse, Philippe Chaudier, Lucie Louboutin, Quentin Ode, Adrien Van Haecke, Marcelle Mercier, Vincent Belgaid, Arnaud Walch, Sébastien Martres, Franck Trouillet, Cédric Barrey, Ali Mojallal, Sophie Brosset, Camille Hanriat, Hélène Person

Microbiologists – Frederic Laurent, Céline Dupieux, Laetitia Berraud, Camille Kolenda, Jérôme Josse, Tiphaine Roussel-Gaillard

Nuclear Medicine – Isabelle Morelec, Marc Janier, Francesco Giammarile PK/PD specialists – Michel Tod, Marie-Claude Gagnieu, Sylvain Goutelle Clinical Research Assistant – Eugénie Mabrut







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