# Phage therapy in patients with complex bone and joint infection

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DELVON















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



Le Journal de Médecine de Lyon

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

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





Clinique des Maladies Infectieuses, Hôpital de la Croix-Rousse Hospices Civils de Lyon 1958-1960





Bactériophages thérapeutiques préparés à l'Institut Pasteur de Lyon dans les années 1970

#### Academic collaboration

Pr. Bertoye

Pathogenic bacteria from the patient

978

#### Infectious Disease clinic

**Institut Pasteur** 

Lyon

Active and trained

bacteriophages



# Large production of antibiotics in 1970-1980 killed the phage therapy

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- Large spectrum
- Bactericidal activity
- Oral and IV
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# Lessons to be learned of phage therapy of the 20<sup>th</sup> century





#### Docteur André RAIGA

Ancien Interne lauréat des Hôpitaux Ex-Chef de Clinique chirurgicale à la Faculté

H 10 H

At the stage of bone necrosis, it will only succeed in stopping the progression of the infection, but it will be able to do nothing against the dead bone deprived of circulation; this bone will become sequestered and the lesion only needs surgery. To do otherwise is to commit, in my opinion, an error of therapeutic indication.

Au stade de nécrose osseuse, il ne réussira plus qu'à enrayer la progression de l'infection, mais il ne pourra plus rien contre l'os que la mort a privé de circulation ; cet os va se séquestrer et la lésion ne relève plus maintenant que de la chirurgie. Agir autrement c'est commettre, à mon sens, une erreur d'indication thérapeutique. 1961

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# Partial bone necrosis requiring <u>surgery</u>

Skin and soft tissue damage requiring surgical coverage



PHAGE THERAPY CAN NOT REPLACE SURGERY

Ferry T.

НС

HOSPICES CIVILS

Patient with a relapsing infection after Phage therapy in Tbilissi

#### Cocktails produced in 2019 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)



Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial









# Lessons to be learned of phage therapy of the 20<sup>th</sup> century

- Use <u>GMP</u> or <u>'GMP-like'</u> bacteriophages (IV use) <a>2.0</a>
- "Ready-to-use" phage cocktails for "easy-to-treat" bacterial infections (commercial use) <u>Prêt-à-porter</u>
- Personalize phage therapy in patients with severe bacterial infection <u>Sur-mesure</u>



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- Academic collaborations (lab. and clinic) to phage banking, susceptibility, training and administration
- Particular interest for patients infected with <u>antibiotic-</u> resistant bacteria
- <u>Do not use it alone</u> in bone and joint infection in patients with bone necrosis

#### **REFERENCE CENTERS FOR THE MANAGEMENT OF BONE AND JOINT INFECTION**



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Orthop Traumatol Surg Res. 2019 Feb;105(1):185-190.

### **Declaration of Helsinki**



**Special Communication** 

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



Wori d

MEDICAL

World Medical Association

- Unproven Interventions in Clinical Practice
- 37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, <u>May use</u> an <u>Unproven</u> intervention if in the physician's judgement it offers hope of <u>saving life</u>, <u>re-establishing health</u> or alleviating suffering. In France: <u>compassionate</u> use, magistral preparation by the hospital pharmacist

#### **Clinical case #4**

# Amputation (but not feasible !) ?

PRO VS. CON

#### 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 ?



#### Lyon Phage team













"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. <u>'Debridement And Implant Retention' (DAIR)</u> with local administration of personalized cocktail of bacteriophages (PhagoDAIR) followed by suppressive antibiotherapy as salvage therapy in patients with relapsing prosthetic knee infection



**Conclusions:** Personalized bacteriophage therapy has the potential to be used as salvage therapy during DAIR in patients with relapsing *S. aureus* and *P. aeruginosa* prosthetic knee infection, to improve the efficacy of suppressive antibiotics, and to avoid considerable loss of function.

<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 case #5**

74-year-old man

Melanoma treated with anti-PD1

Catheter-related *P. aeruginosa* bacteriemia in January 2018

Spinal pain summer 2018

Spondylodiscitis with spinal abscess

Pandrug-resistant P. aeruginosa in culture!



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	Pseudomonas aeruginosa CMI (mg/l)
Ticarcilline + Ac. Clav	R (> 64)
Pipéracilline	R (> 64)
Pipéracilline + Tazobactam	R (> 64)
Ceftazidime	R (> 32)
Céfépime	R (> 32)
Aztréonam	R (> 32)
Imipénème	R (> 8)
Meropeneme	R (> 8)
Gentamicine	R (> 8)
Tobramycine	R (> 8)
Amikacine	R (> 32)
Ciprofloxacine	R (> 2)
Lévofloxacine	R (> 4)
Cotrimoxazole	R
Colistine	S (8) 📥 R
Colistine (Etest)	S E-test∶1 ➡> R
Ceftolozane-tazobactam (Etest)	R E-test : > 256
Ceftazidime-Avibactam (Etest)	R

E-test: 64

The strain was also spontaneously resistant to GMP bacteriophages !!!

PHERECYDES

PHARMA

AMPLIPH

#### **Potential European academic collaborations**



#### Potential European academic collaborations ansm



#### Potential European academic collaborations ansm





#### Potential European academic collaborations answ



#### Under the supervision of **Potential European academic collaborations**



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Personalized production and administration of bacteriophages: lessons learned from a <u>unique European academic collaboration</u> to treat a patient with pandrug-resistant spinal *P. aeruginosa* infection





UNIL | Université de Lausanne

Under the supervision of Agence nationale de sécurité du médicament et des produits de santé French Health Authority



30th ECCMID Paris, France 18-21 April 2020

CRICAC

**Conclusions:** Personalized phage therapy is a potential adjunct treatment for patients with complex BJI due to pandrug-resistant bacteria. **In addition to industrial phages under development, academic collaborative research is crucial to develop personalized phage therapy.** 



 Crucial need for (alternatives) <u>additional therapies</u> <u>to antibiotics</u> to maximize clinical success in complex bacterial infections





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- Don't forget <u>Lessons from 20<sup>th</sup> century</u>







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- Need for national phage therapy center(s)









#### Lyon BJI Study group

#### **Coordinator: Tristan Ferry**

Infectious Diseases Specialists – Tristan Ferry, Florent Valour, Thomas Perpoint, Florence Ader, Sandrine Roux, Claire Triffault-Philit, 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, Eliott 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

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







Centre International de Recherche en Infectiologie



#### **Croix-Rousse Hospital**









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#### http://www.crioac-lyon.fr



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- All recommendations
- Newsletter





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