Exemple de recherche translationnelle : la phagothérapie

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Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS UMR5308, ENS de Lyon, UCBL1, Lyon, France
Clinical officer ESCMID Study group for Non-Traditional Antibacterial therapy (ESGNTA)
Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)

Président du Comité Scientifique des CRIOAc 2017-2022

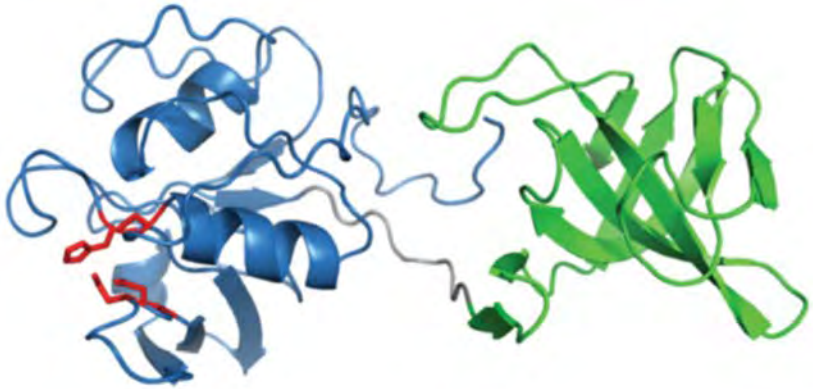
Lyon 1 CRIOAc LYON PHAGE*in*LYON ESGNTA ESCMID STUDY GROUP FOR NON-TRADITIONAL ANTIBACTERIAL THERAPY European Society of Clinical Microbiology and Infectious Diseases ciri Centre International de Recherche en Infectiologie HCL HOSPICES CIVILS DE LYON

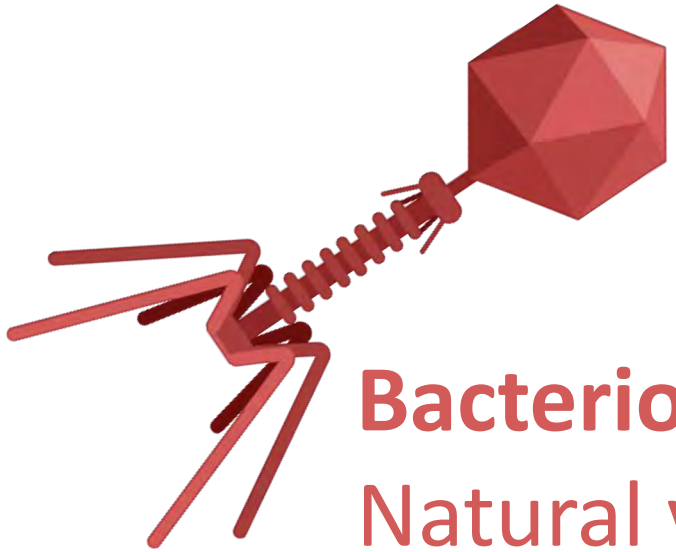
Non traditional anti-bacterial therapy

World Health Organization

Lysins

Biological “natural” enzymes





Bacteriophages

Natural viruses

Clinical officer

ESGNTA

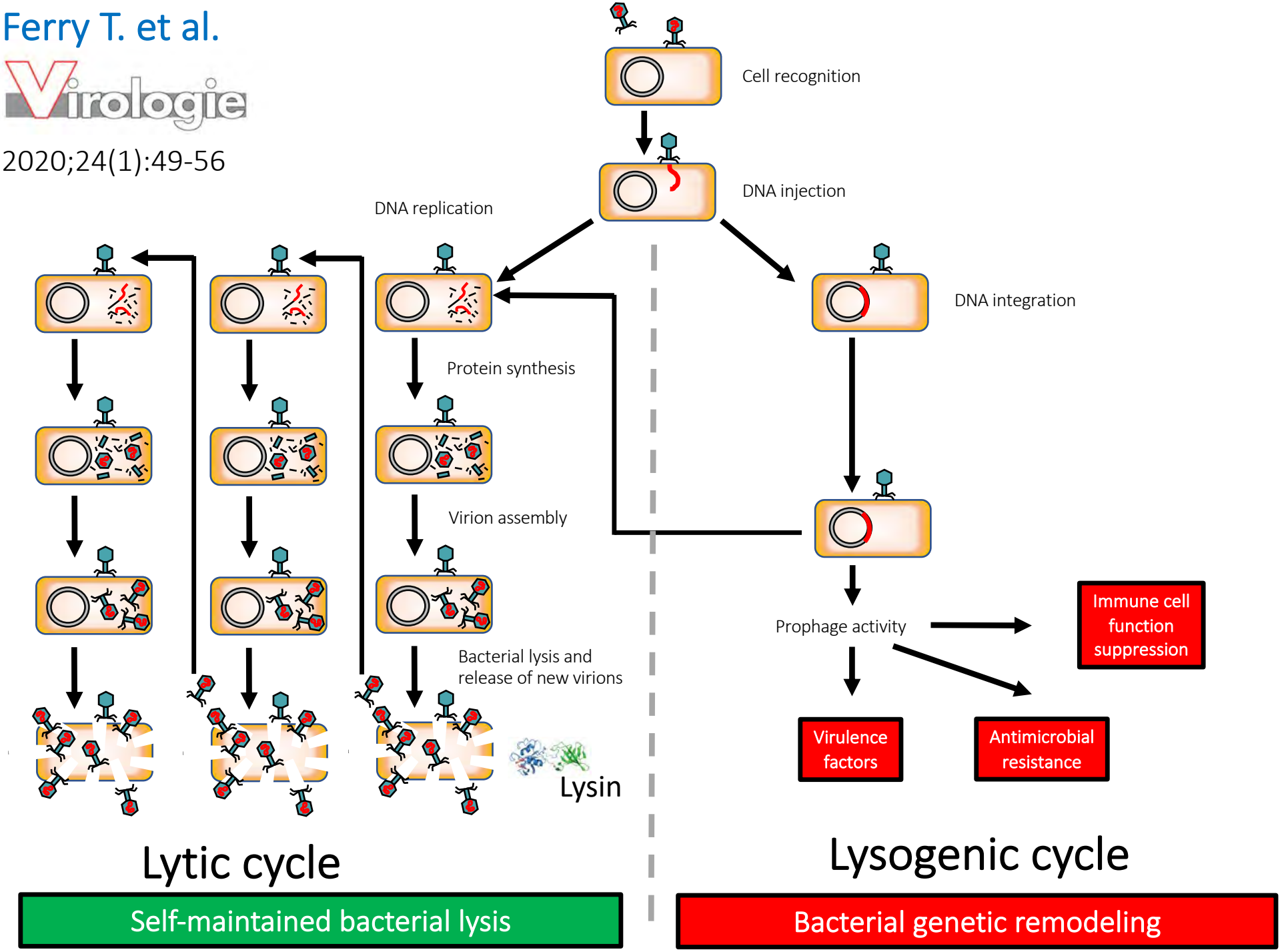
ESCMID STUDY GROUP FOR NON-TRADITIONAL ANTIBACTERIAL THERAPY

European Society of Clinical Microbiology and Infectious Diseases

Ferry T. et al.

Virologie

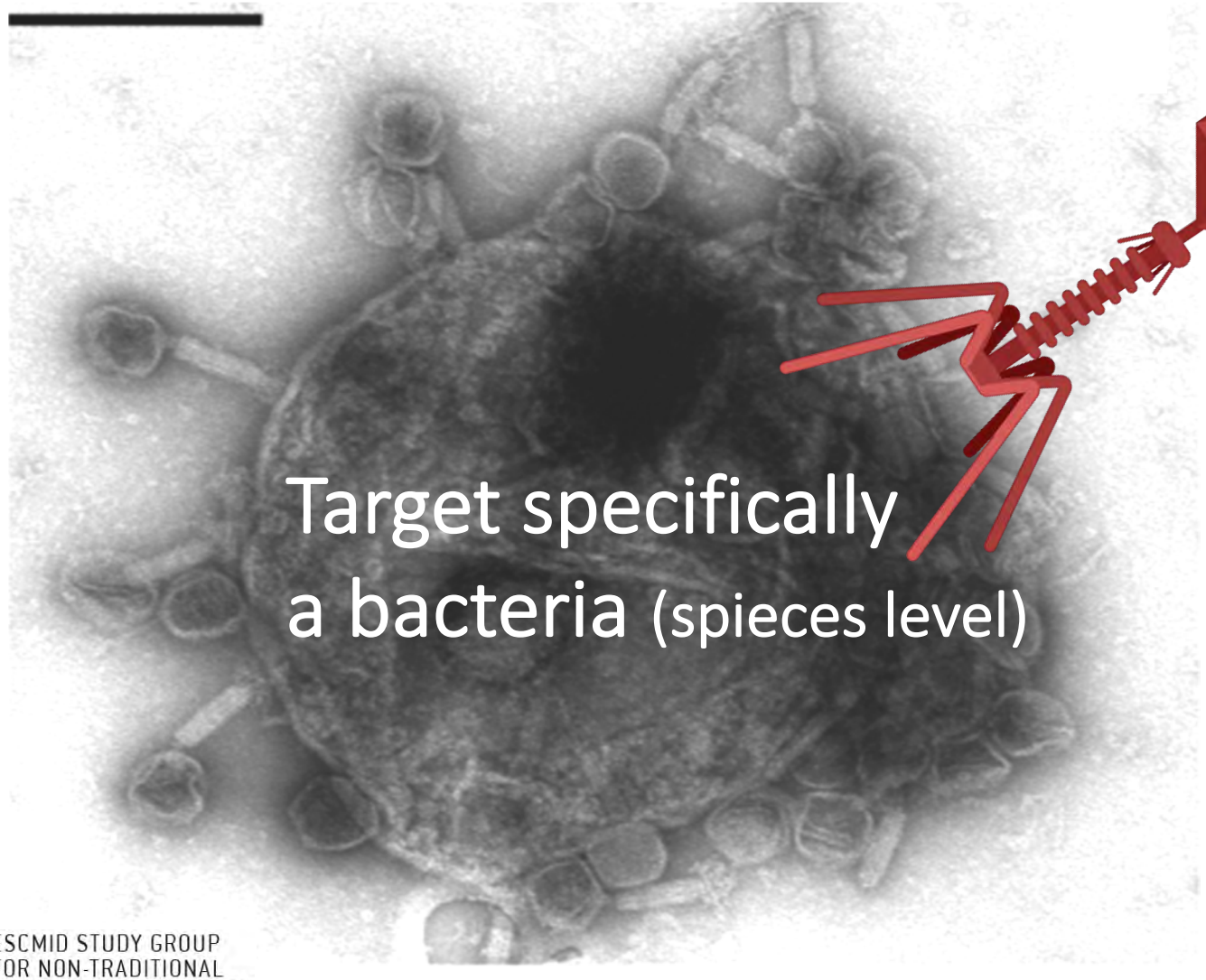
2020;24(1):49-56



Bacteria have also their pandemia!

World Health Organization

Non-**T**raditional
Antibacterial
therapy



Target specifically
a bacteria (spieces level)

Each virus

FONDATION HCL HOSPICES CIVILS DE LYON

PHAGE*in*LYON
Clinic

ESGNTA ESCMID STUDY GROUP FOR NON-TRADITIONAL ANTIBACTERIAL THERAPY
European Society of Clinical Microbiology and Infectious Diseases

Merabishvili et al. *PloS ONE* 2009

Le Journal de Médecine de Lyon

After d'Herelle, The story continued in Lyon

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

Par MM. André Bertoye et A.-L. Courtieu.

Les bacilles pyocyaniques sont fréquemment résistants aux antibiotiques usuels, otitiqu… attribuées semble être en augmentation. Leur caractère rebelle est une de leurs caractéristiqu… différente de … l'existence de … de stock-bact… tation par sélection … permet … nutritif … indispen… pouvoir … intravei… Un … cette publication.

Antimicrobial resistance

Phage banking
Phage training

Meningitis
Skin and soft tissue
Bone and joint infection

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

1958-1960

Méningite purulente à colibacilles traitée par un bactériophage adapté intrarachidien

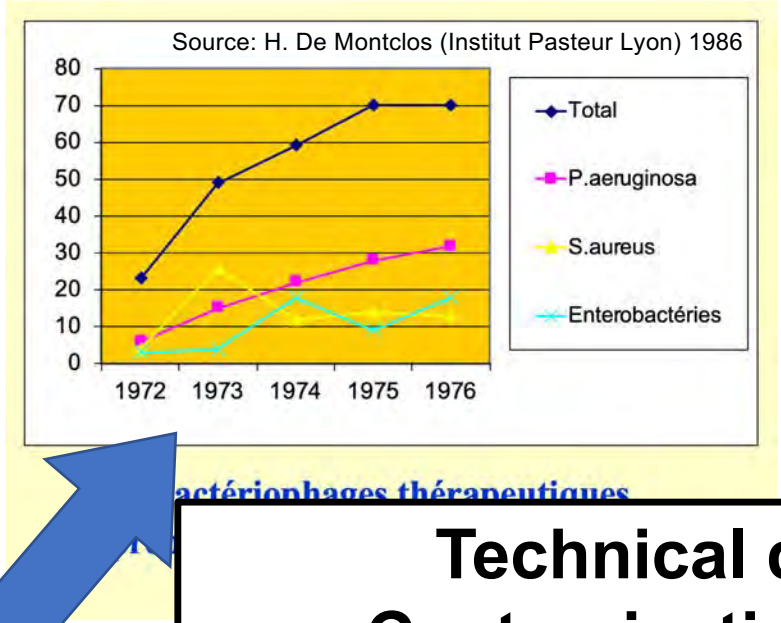
Par MM. P. SEDALLIAN, A. BERTOYE, J. GAUTHIER. J.-M. MULLER et A.-L. COURTIEU.

Clinique des Maladies Infectieuses et Institut Pasteur de Lyon

Une injection intrarachidienne d'1/10 de centimètre cube n'ayant été suivie d'aucun accident, on commence, dès le lendemain 30 septembre, le traitement aux doses thérapeutiques : 1 centimètre cube de bactériophage intraventriculaire et 1 centimètre cube intrarachidien par vingt-quatre heures. Rapidement, le nombre des éléments du liquide céphalo-rachidien s'effondre à 356 contre 1.800 deux jours auparavant. Dès lors, la situation va s'améliorer très vite et on peut espérer la partie gagnée, malgré la persistance dans le liquide céphalo-rachidien d'un taux d'albumine aux alentours d'un gramme et de 50 à 200 éléments.

A une demande de **M. Roche, M. Bertoye** précise que nombre de germes peuvent être dotés d'un bactériophage. Il faut quatre à cinq jours pour l'adaptation du bactériophage : ce ne peut donc pas être une médication d'urgence.

Lyon Med. 1958 Mar 30;90(13):509-12



L'INSTITUT BACTÉRIOLOGIQUE DE LYON

Lyon Pasteur Institute

Active and trained bacteriophages

Technical development
Customisation of treatment
Academic multidisciplinary approach
70 patients/year!

Isolation of the isolates responsible for the infection

Infectious diseases clinic

HCL
HOSPICES CIVILS DE LYON

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

Patrick Jault, Thomas Leclerc, Serge J
Ronan Le Floch, Jean Vivien Schaal, C

2: Time to observe reduction
Kaplan-Meier analysis of median time
highest daily bacterial burden compared with day 0. HR=hazard ratio. PP1131=cocktail of 12 natural lytic anti-*Pseudomonas aeruginosa* bacteriophages.

COMPASSIONATE USE

...osa

...RECYDES
...RMA

Lancet Infect Dis 2018

PHOSA

PHERECYDES PHARMA

PHOSA & Phagothérapie | Consortium PHOSA | Communication | Contact

CRIOAC LYON

PHERECYDES PHARMA

<u>Phage discovery</u>
to find active bacteriophages against Staphylococci

Vivexia laboratory

HCL HOSPICES CIVILS DE LYON

ciri Centre International de Recherche en Infectiologie

CENTRE HOSPITALIER INTERCOMMUNAL VILLENEUVE-SAINT-GEORGES Lucie & Raymond AUBRAC

Phages anti-S. aureus

Efficacy of Bacteriophages in a *Staphylococcus aureus* Nondiabetic or Diabetic Foot Infection Murine Model

S. Albac,[a] M. Medina,[b] D. Labrousse,[a] D. Hayez,[a] D. Bonnot,[a] N. Anzala,[a] F. Laurent,[c] T. Ferry,[d] A. Dublanchet,[e] P. Chavanet,[a,f] C. Fevre,[b] D. Croisier[a]

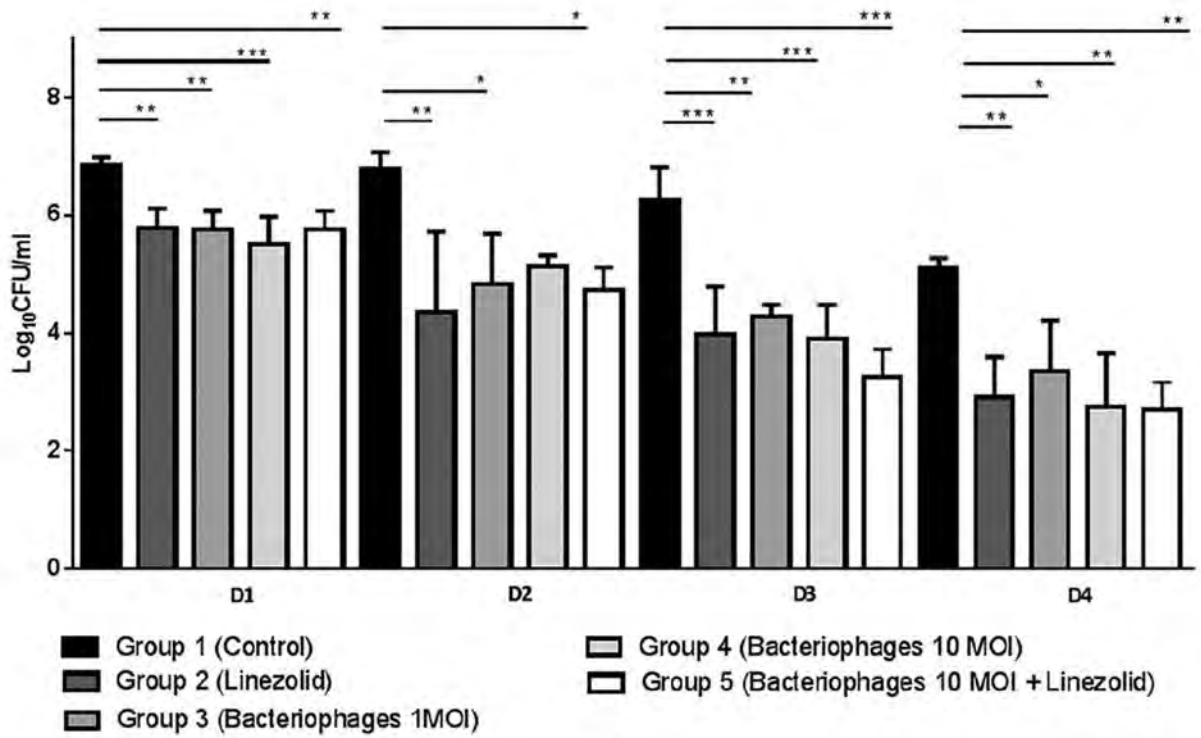


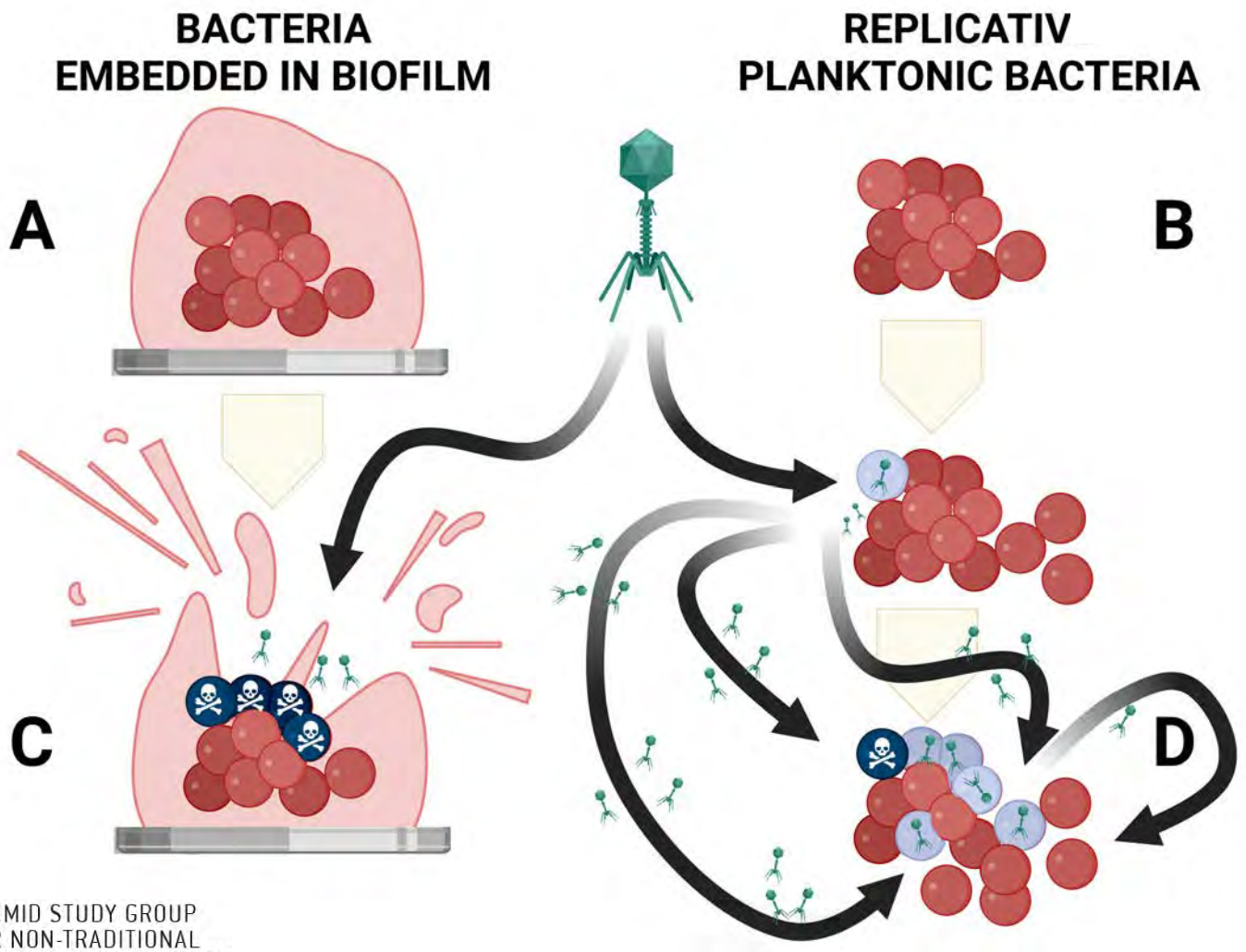
FIG 2 Bacterial load (log_{10} CFU/ml), in hindpaws of nondiabetic BALB/c mice ($n = 4$/group and time point) after treatment with an assembly of three bacteriophages (1 or 10 MOI), linezolid (25 mg/kg i.p.), and the combination of phages plus linezolid. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Bacteria have also their pandemia!

World Health Organization

Non-**T**raditional
Antibacterial
therapy



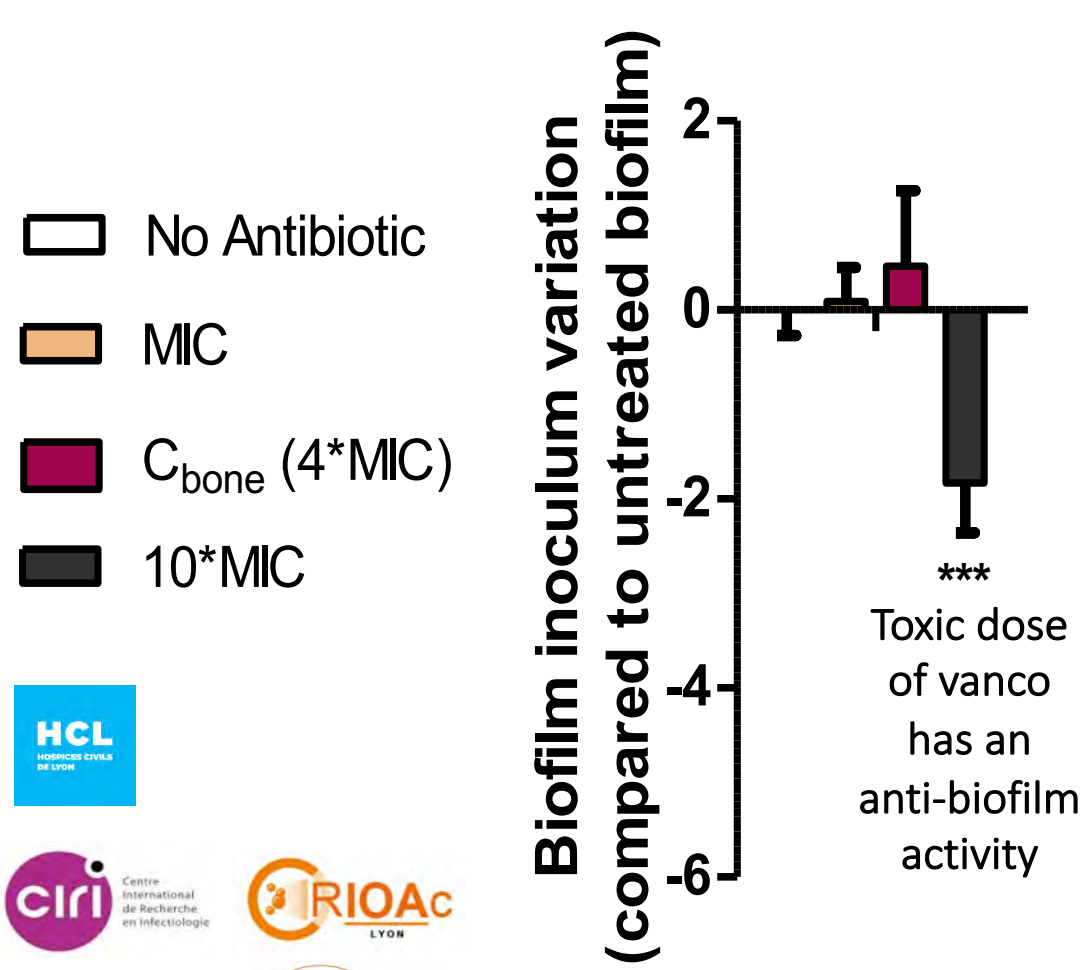
FONDATION HCL HOSPICES CIVILS DE LYON

PHAGE*in*LYON *Clinic*

ESGNTA ESCMID STUDY GROUP FOR NON-TRADITIONAL ANTIBACTERIAL THERAPY
European Society of Clinical Microbiology and Infectious Diseases

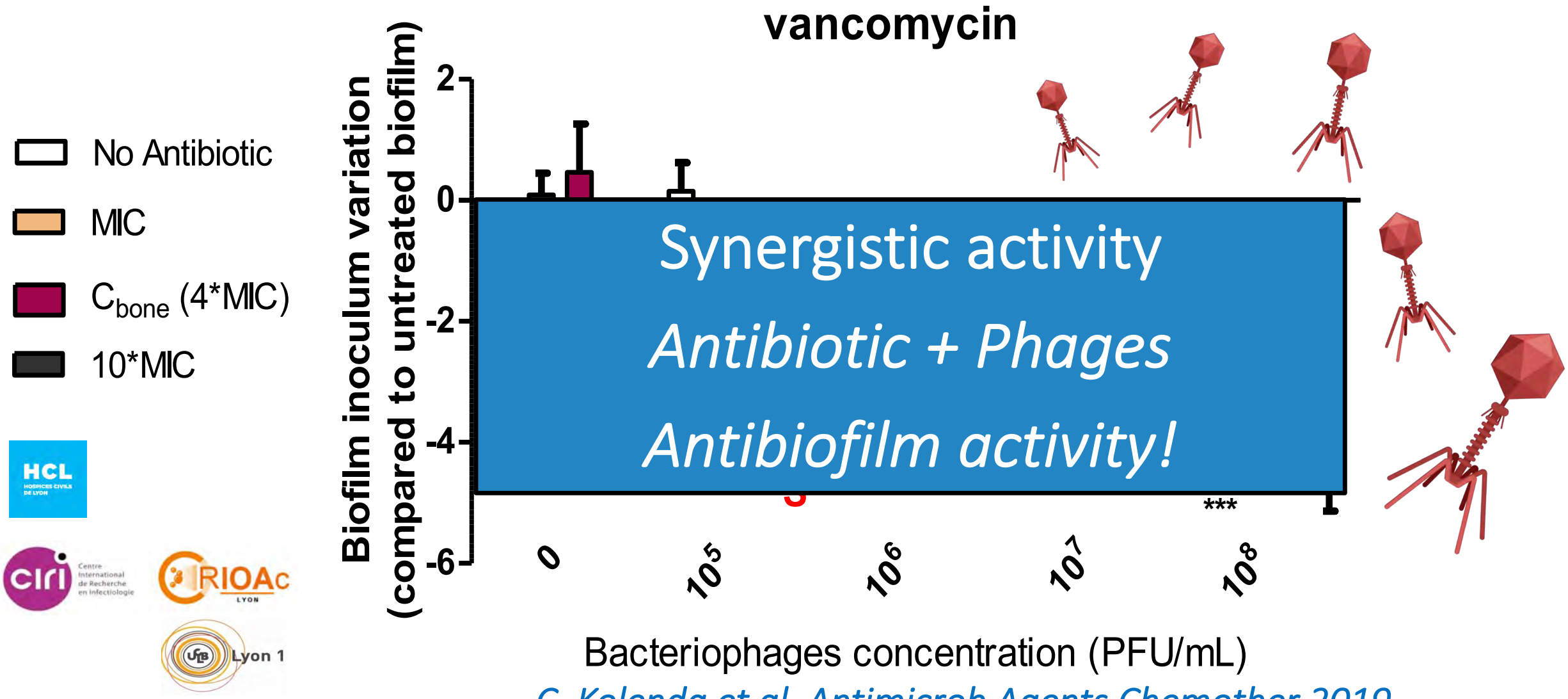
T. Ferry. Springer 2023 In press

Phages have antibiofilm activity



C. Kolenda et al. Antimicrob Agents Chemother 2019

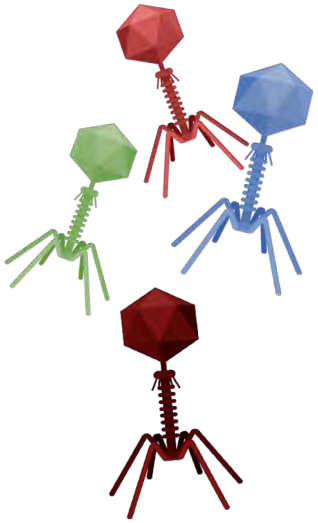
Phages have antibiofilm activity



C. Kolenda et al. Antimicrob Agents Chemother 2019

Développement de la phagothérapie à Lyon

PHAGE*in*LYON



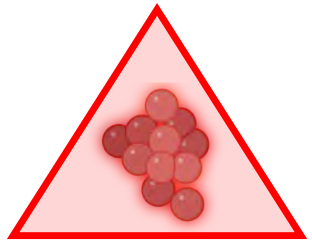
PHAGE*in*LYON Clinic

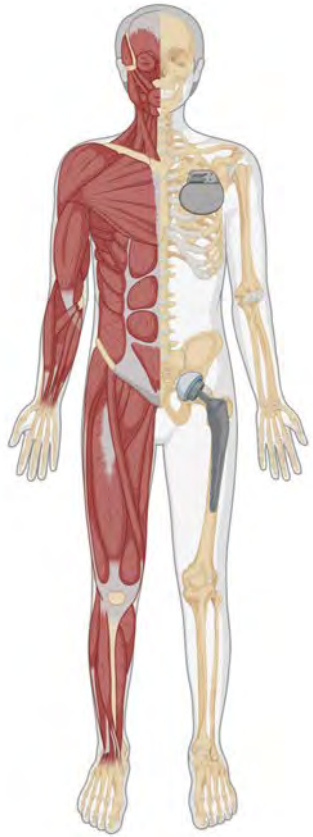
Tristan Ferry

T. Ferry

Développement clinique
RCP CRIOAc Thérapies innovantes
RCP Phagothérapie
Validation des indications
Prise en charge des patients
Etudes de cohortes
Essais thérapeutiques

A large panel of **severe** bacterial infections





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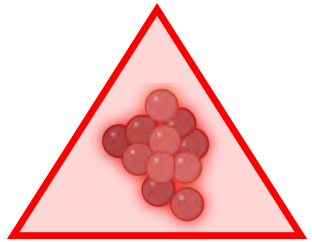


Central nervous system infections

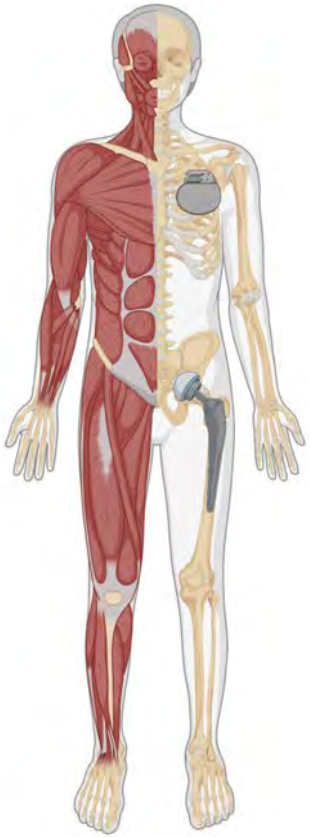
Implant-associated meningitis

Lung infections

Ventilator-associated pneumonia
Exacerbation in cystic fibrosis
Exacerbations in bronchiectasis

Urinary tract infections

Pyelonephritis
Ureteral stent-associated infection



Cardiovascular infections

Endocarditis
Cardiac electronic device infection
Prosthetic-valve endocarditis
Vascular graft infection

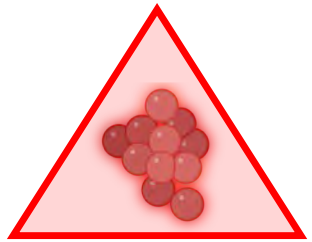
Muskuloskeletal infections

Wound infection
Osteomyelitis, fracture-related infection
Implant-associated bone and joint infection
Prosthetic joint infection

Digestive-tract infections

Typhoid fever, shigellosis
Cholera

A large panel of **severe** bacterial infections



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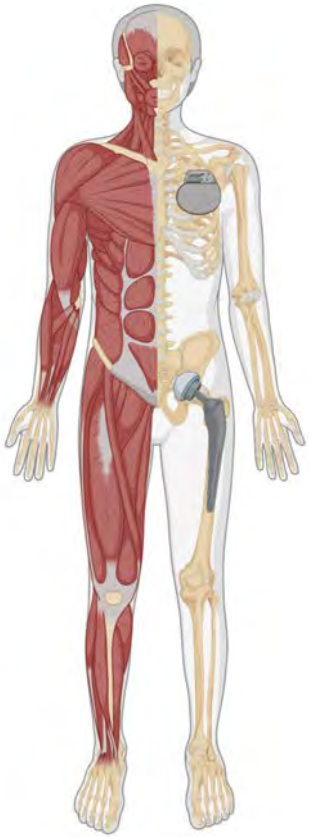

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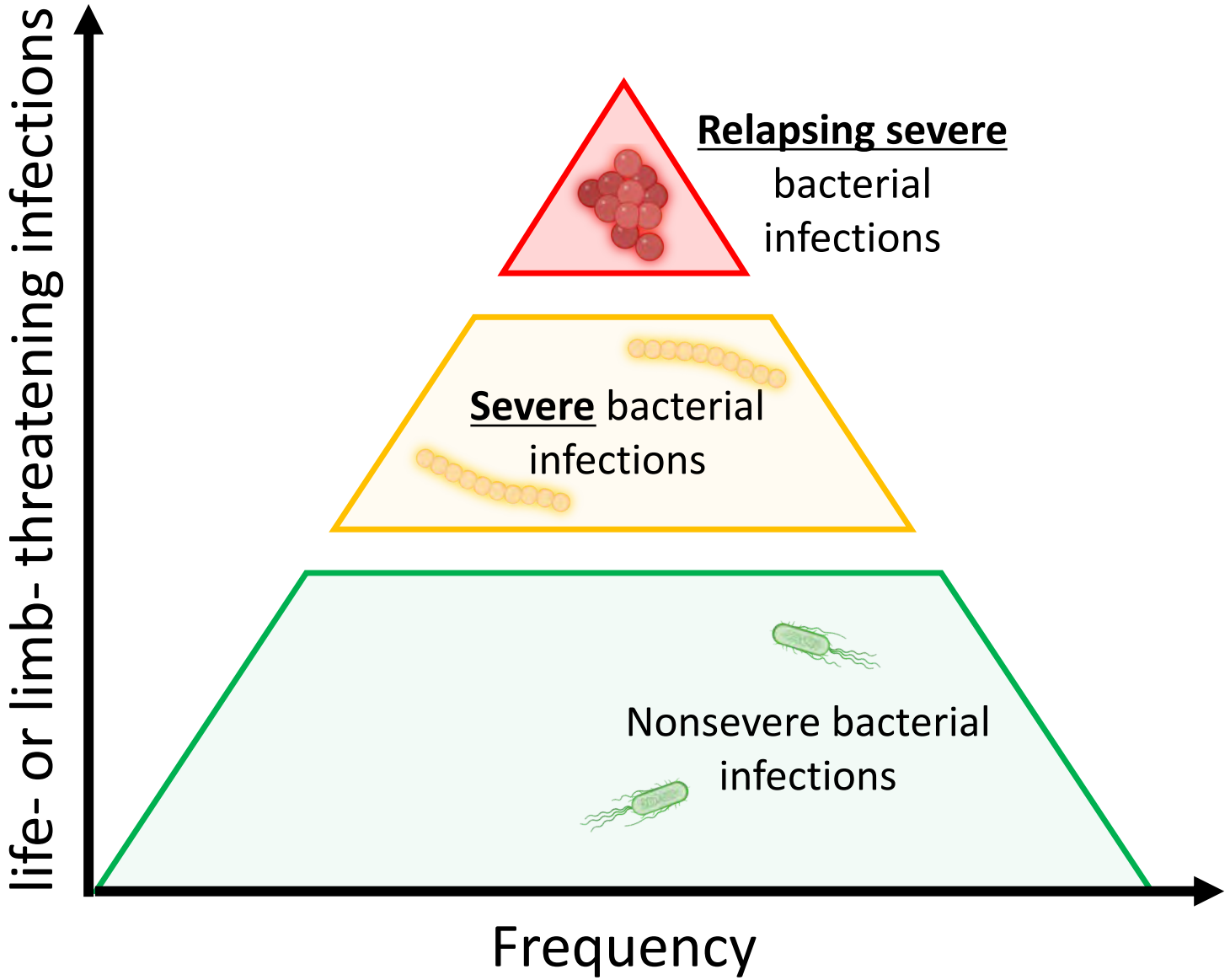
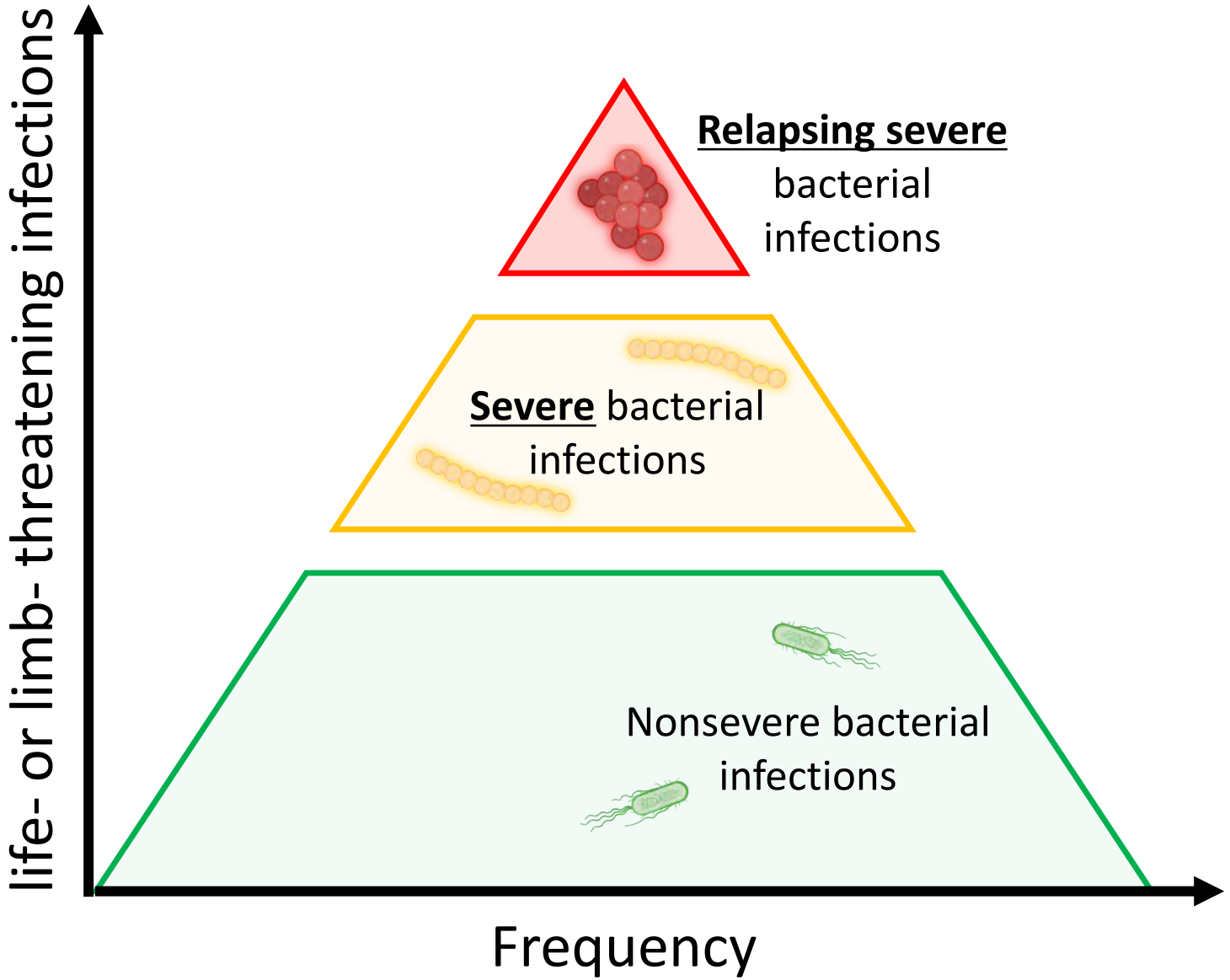
The pyramid of bacterial infectious diseases



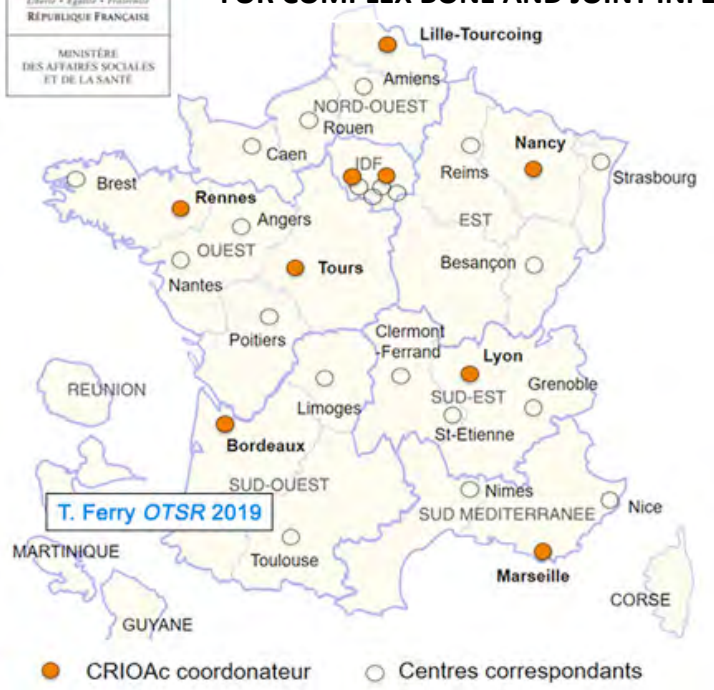
The pyramid of bacterial infectious diseases



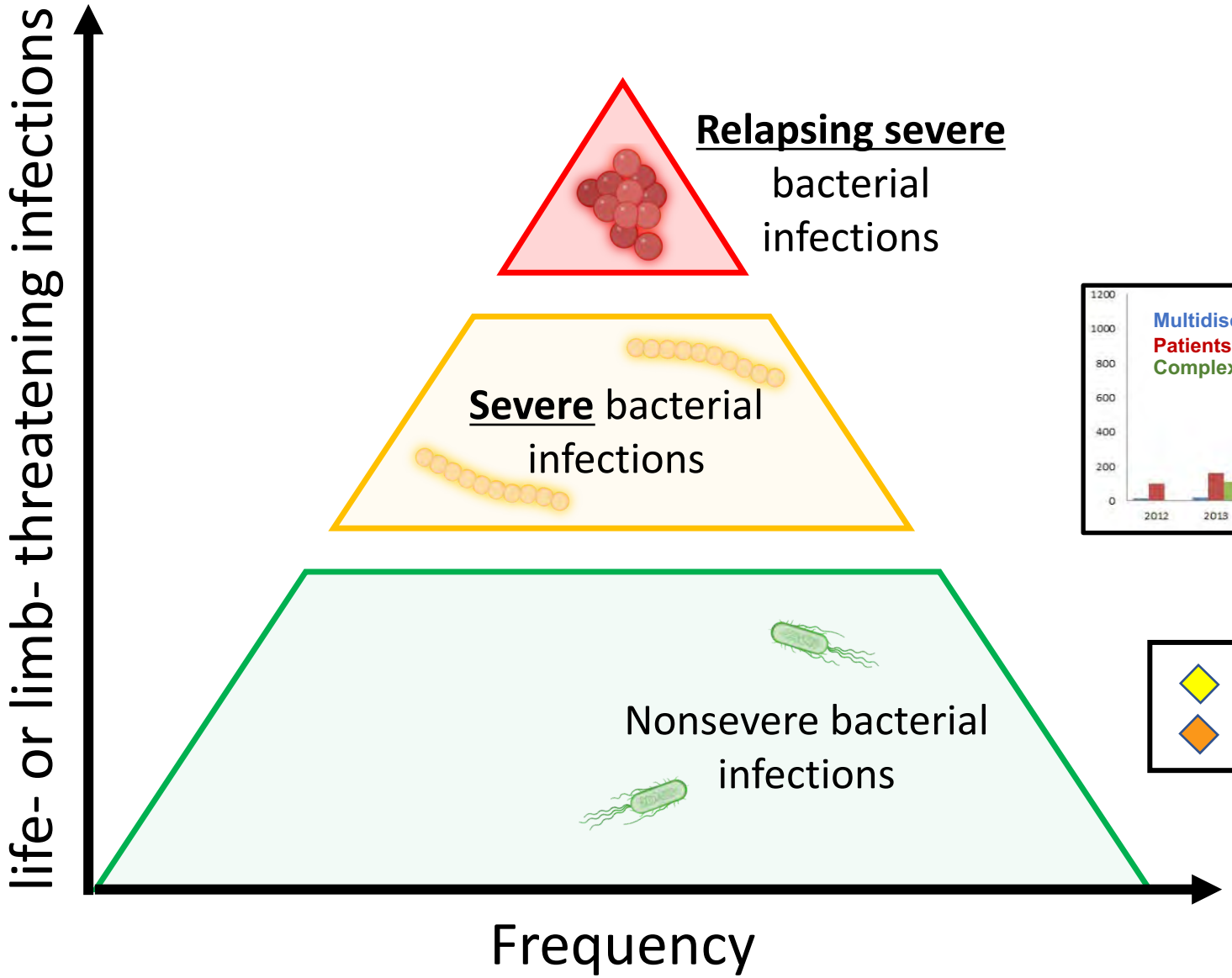
CRIOAc LYON

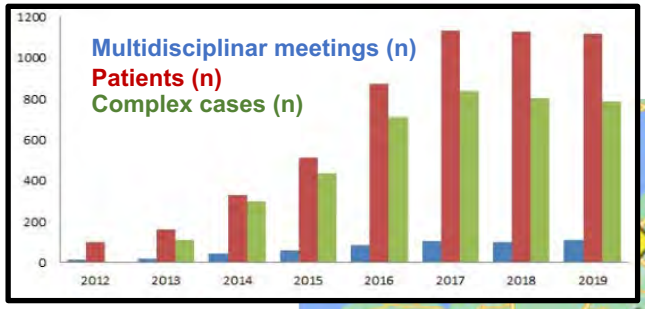
HCL HOSPICES CIVILS DE LYON

DEDICATED NETWORK
FOR COMPLEX BONE AND JOINT INFECTIONS

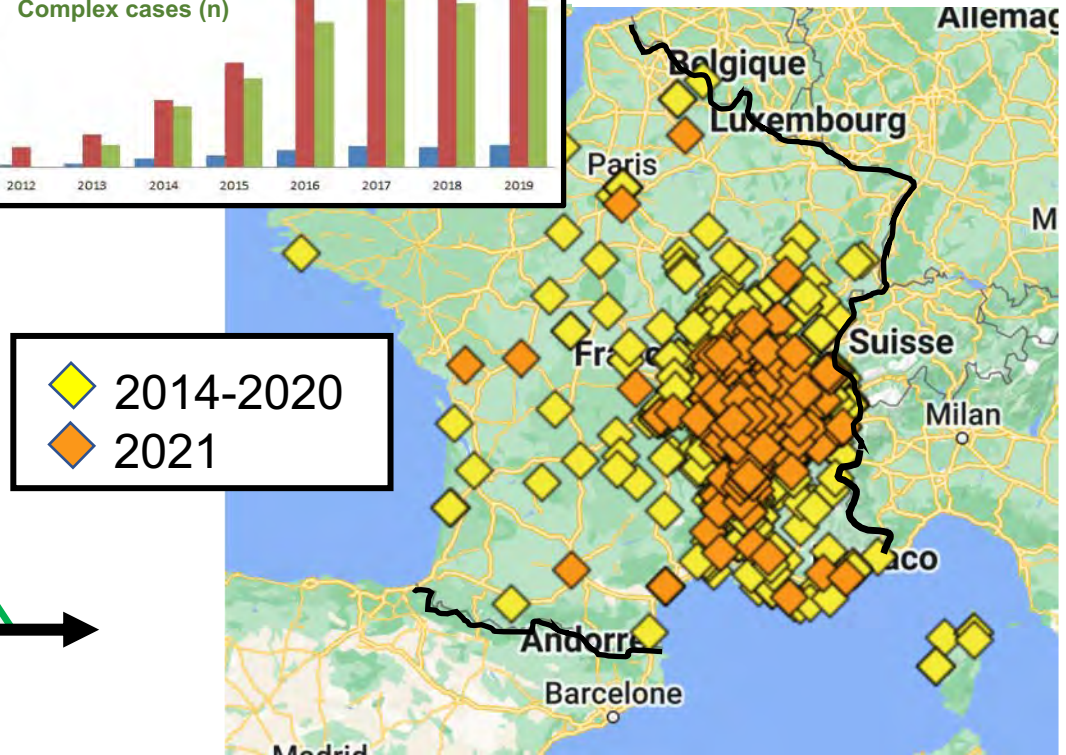


The pyramid of bacterial infectious diseases

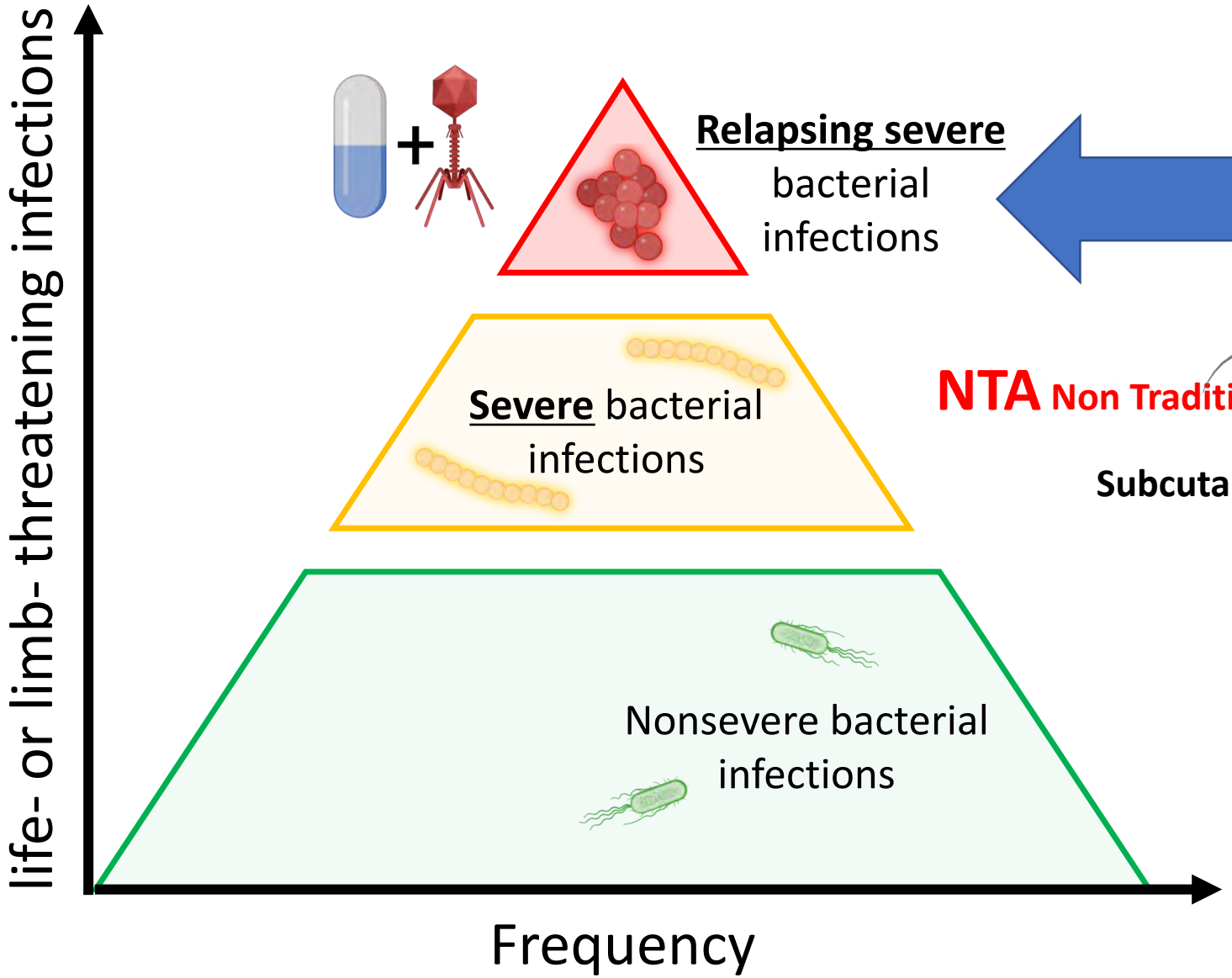




PATIENT'S RESIDENCE



The pyramid of bacterial infectious diseases



PHAGE*in*LYON

CRIOAc LYON

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NTA Non Traditionnal Anti-bacterial therapies (phages and lysins)

Subcutaneous suppressive therapies

Antibiotics-loaded bone substitutes

Antibiotics-loaded cements

New antibiofilm drugs

viruses

Lyon BJI study group

PHAGE*in*LYON

MDPI

Review

Past and Future of Phage Therapy and Phage-Derived Proteins in Pat

Tristan Fe
Jérôme Jos
Frédéric L
on behalf

REVIEW ARTICLE OPEN ACCESS

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

Tristan Ferry[1,2,3,4,*], Cécile Batailler[2,3,5], Sophie Brosset[2,3,6], Camille Kolenda[2,3,4,7], Sylvain Goutelle[2,3,8,9], Elliot Sappey-Marinier[2,3,5], Jérôme Josse[2,3,4,7], Frédéric Laurent[2,3,4,7], Sébastien Lustig[2,3,5], On Behalf of the Lyon BJI Study Group,[a]

Virologie

t une infection ostéoarticulaire : historique, fondements, faisabilité et perspectives en France

Phage therapy in bone and joint infection: history, rationale, feasibility and perspectives in France

Case Report: Arthroscopic "Debridement Antibiotics and Implant Retention" With Local Injection of Personalized Phage Therapy to Salvage a Relapsing *Pseudomonas Aeruginosa* Prosthetic Knee Infection

Tristan Ferry[1,2,3,4], Camille Kolenda[2,3,4,5], Cécile Batailler[2,3,6], Romain Gaillard[3,6], Claude-Alexandre Gustave[2,3,4,5], Sébastien Lustig[2,3,6], Cindy Fevre[7], Charlotte Petitjean[7], Gilles Leboucher[8], Frédéric Laurent[2,3,4,5] and the Lyon BJI Study group*

Open Forum Infectious Diseases
BRIEF REPORT

Salvage Debridement, Antibiotics and Implant Retention ("DAIR") With Local Injection of a Selected Cocktail of Bacteriophages: Is It an Option for an Elderly Patient With Relapsing Staphylococcus *aureus* Prosthetic-Joint Infection?

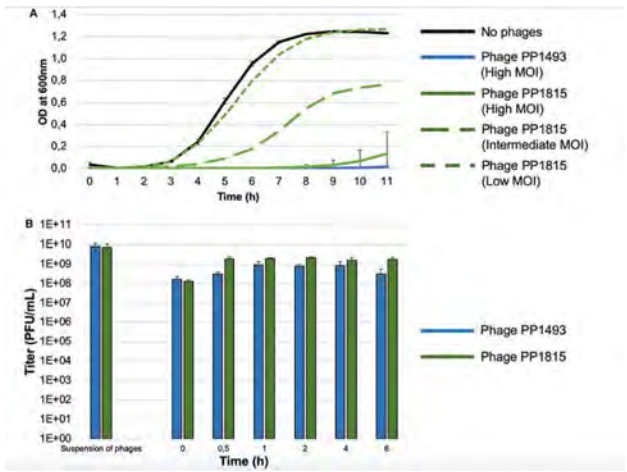
Tristan Ferry,[1,2,3,4] Gilles Leboucher,[5] Cindy Fevre,[6] Yannick Herry,[2,4,7] Anne Conrad,[1,2,3,4] Jérôme Josse,[2,3,4,8] Cécile Batailler,[2,4,7] Christian Chidiac,[1,2,3,4] Mathieu Medina,[6] S. Lustig,[7] and Frédéric Laurent[2,3,4,8]; on behalf of the Lyon BJI Study Group

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 Fevre[7], Jérôme Josse[2,3,4,5], Charlotte Petitjean[7], Christian Chidiac[1,2,3,4], Gilles Leboucher[8] and Frédéric Laurent[2,3,4,5] on behalf of the Lyon BJI Study group*

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 Petitjean[6], Joseph Chateau[7], Cindy Fevre[6], Emmanuel Forestier[8], Sophie Brosset[7], Gilles Leboucher[9], 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*

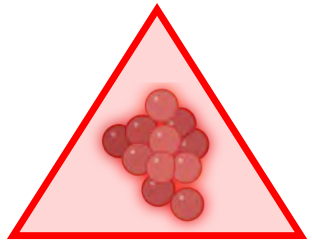


J Antimicrob Chemother 2018; **73**: 2901–2903
doi:10.1093/jac/dky263
Advance Access publication 27 July 2018

Innovations for the treatment of a complex bone and joint infection due to XDR *Pseudomonas aeruginosa* including local application of a selected cocktail of bacteriophages

Tristan Ferry[1–4]*, Fabien Boucher[1,4,5], Cindy Fevre[6], Thomas Perpoint[1,4], Joseph Chateau[1,2,4,5], Charlotte Petitjean[6], Jérôme Josse[2–4,7], Christian Chidiac[1,2–4], Guillaume L'hostis[6], Gilles Leboucher[8] and Frédéric Laurent[2–4,7] on behalf of the Lyon Bone and Joint Infection Study Group[†]

A large panel of **severe** bacterial infections



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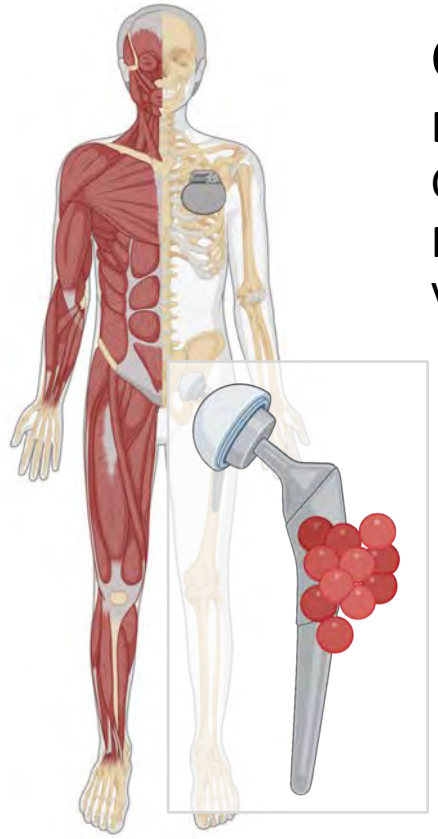

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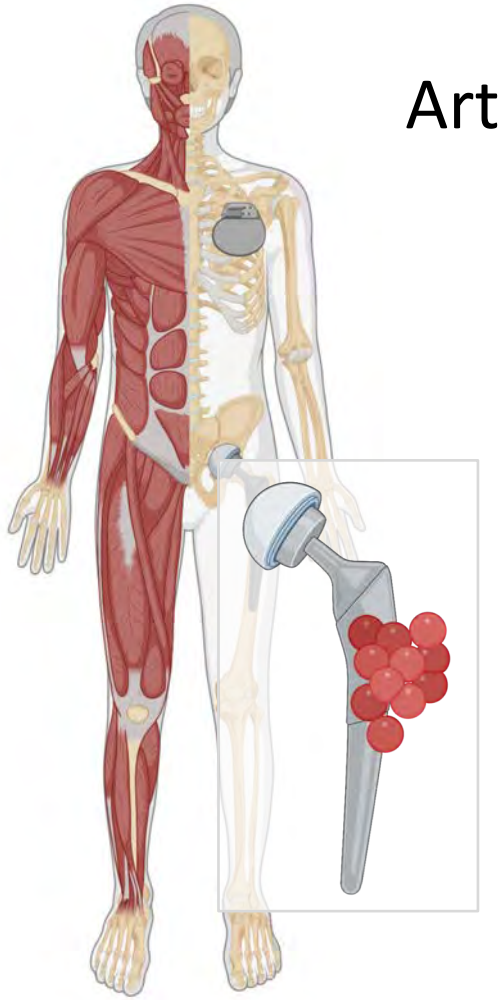
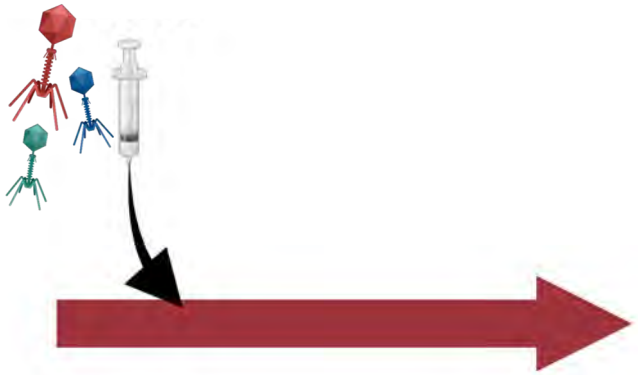
PHAGE *in* LYON

Clinic



Arthroscopic or open

DAIR



Case series RIOAc LYON procedure called « PhagoDAIR »

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 Fevre[7], Jérôme Josse[2,3,4,5], Charlotte Petitjean[7], Christian Chidiac[1,2,3,4], Gilles Leboucher[8] and Frédéric Laurent[2,3,4,5] on behalf of the Lyon BJI Study group*

frontiers in Medicine

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

#PhagoDAIR

Debridement Antibiotics and Implant Retention

Clinical cases (2nd treated patient)

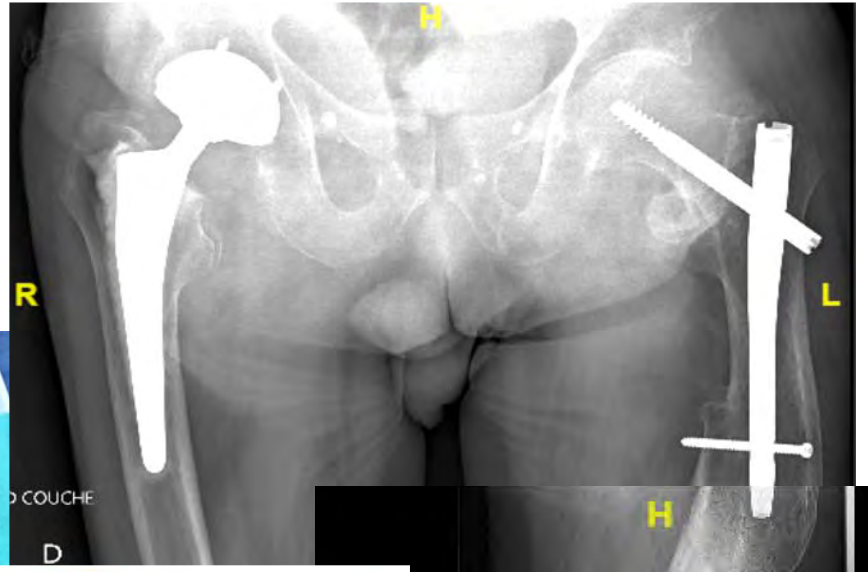
80-year-old man

Relapsing *S. aureus* prosthetic left knee infection (past revision)

Failure

Complex orthopaedic situation with past femoral fracture

Impossible to walk (painful knee)



RIOAc LYON

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Lyon 1

PHAGE*in*LYON

ciri Centre International de Recherche en Infectiologie

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Septic arthritis


Fistula and purulent discharge

“PhagoDAIR”

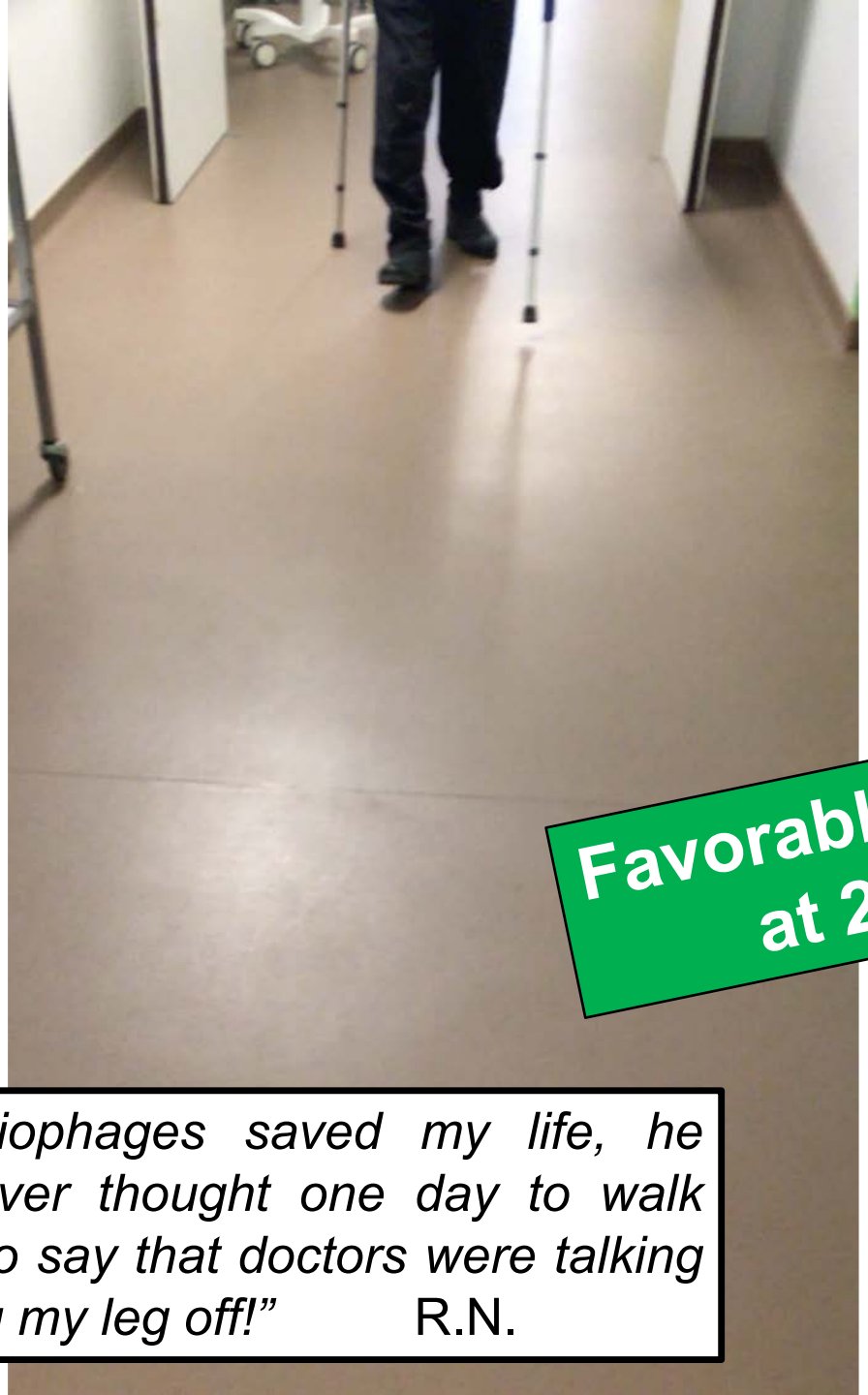
<u>One shot</u> peroperative phage application after “DAIR”

HCL HOSPICES CIVILS DE LYON

PHAGE*in*LYON

FONDATION HCL HOSPICES CIVILS DE LYON

UCBL Lyon 1 — CRIOAc LYON — ciri Centre International de Recherche en Infectiologie



Favorable outcome at 2 years

"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.

PHAGE*in*LYON

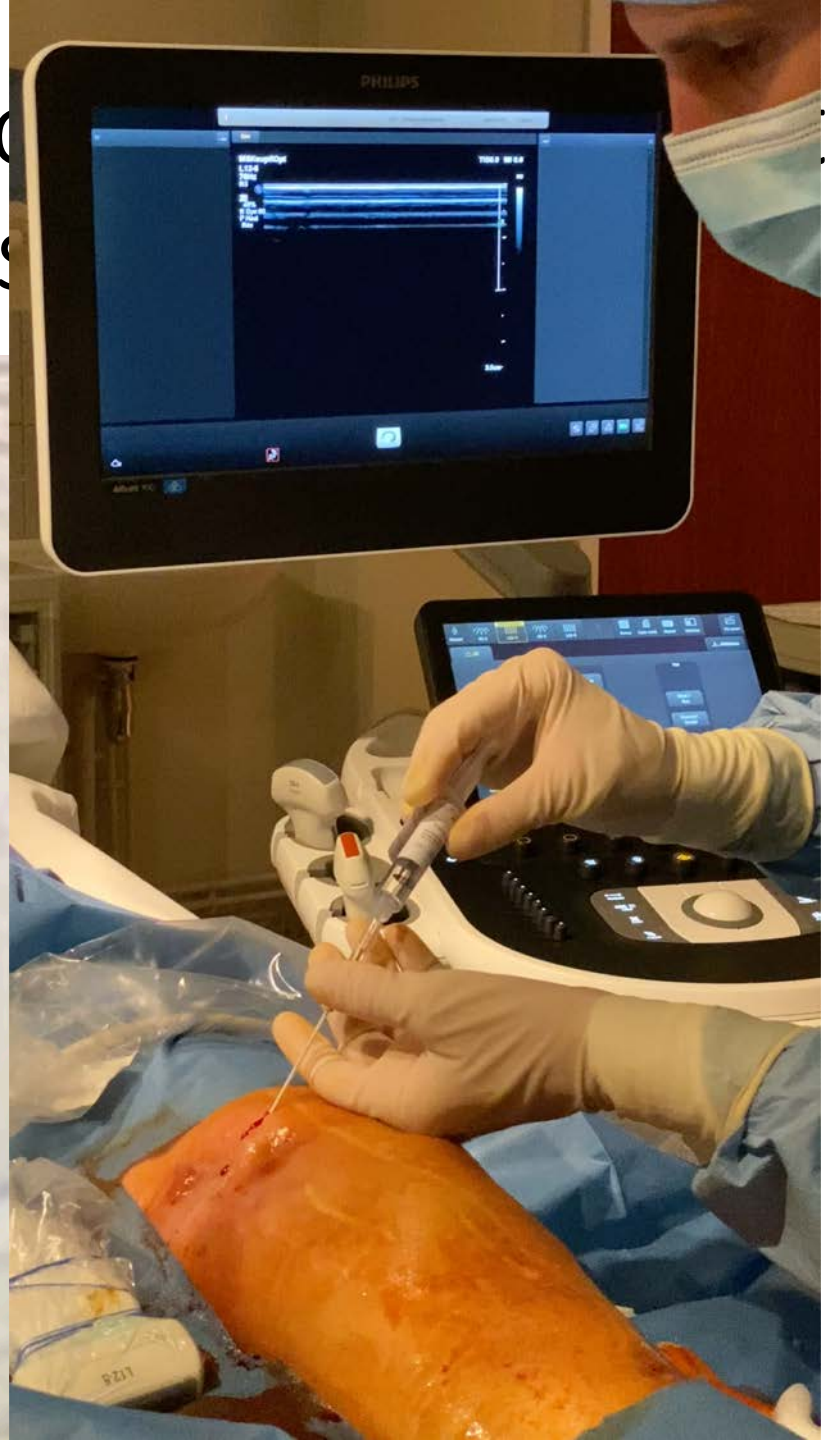
Management of relapsing infections with bacterial persistance

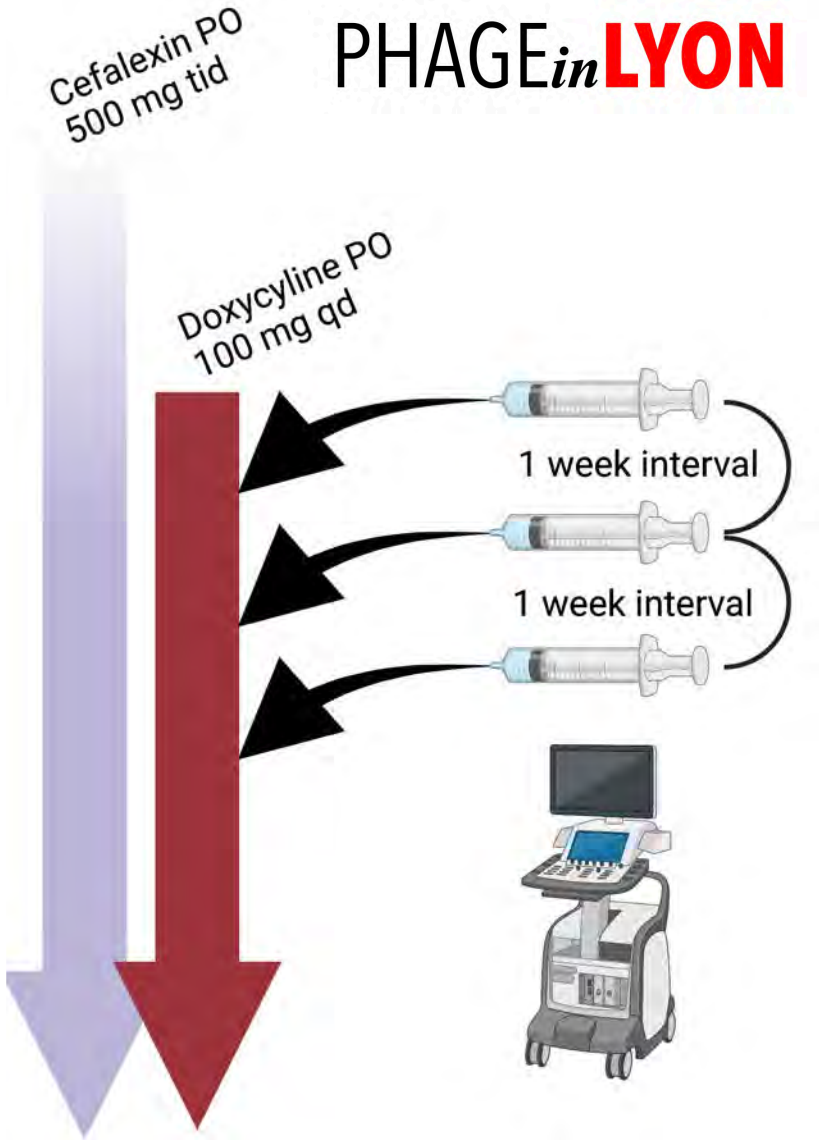
30 months after the PhagoDAIR procedure
Under cefalexin as suppressive therapy

	Staphylococcus aureus CMI (mg/l)
Pénicilline G	R
Oxacilline	S
Kanamycine	S
Gentamicine	S
Tobramycine	S
Erythromycine	S
Lincomycine	S
Pristinamycine	S
Tétracycline	S
Ofloxacine	S
Cotrimoxazole	S
Nitrofurantoine	S
Rifampicine	S
Fosfomycine	S
Acide Fusidique	S
Vancomycine	S
Teicoplanine	S
Linézolide	S

Management of relapsing infections with bacterial persistance

Management c tions with bacterial persis





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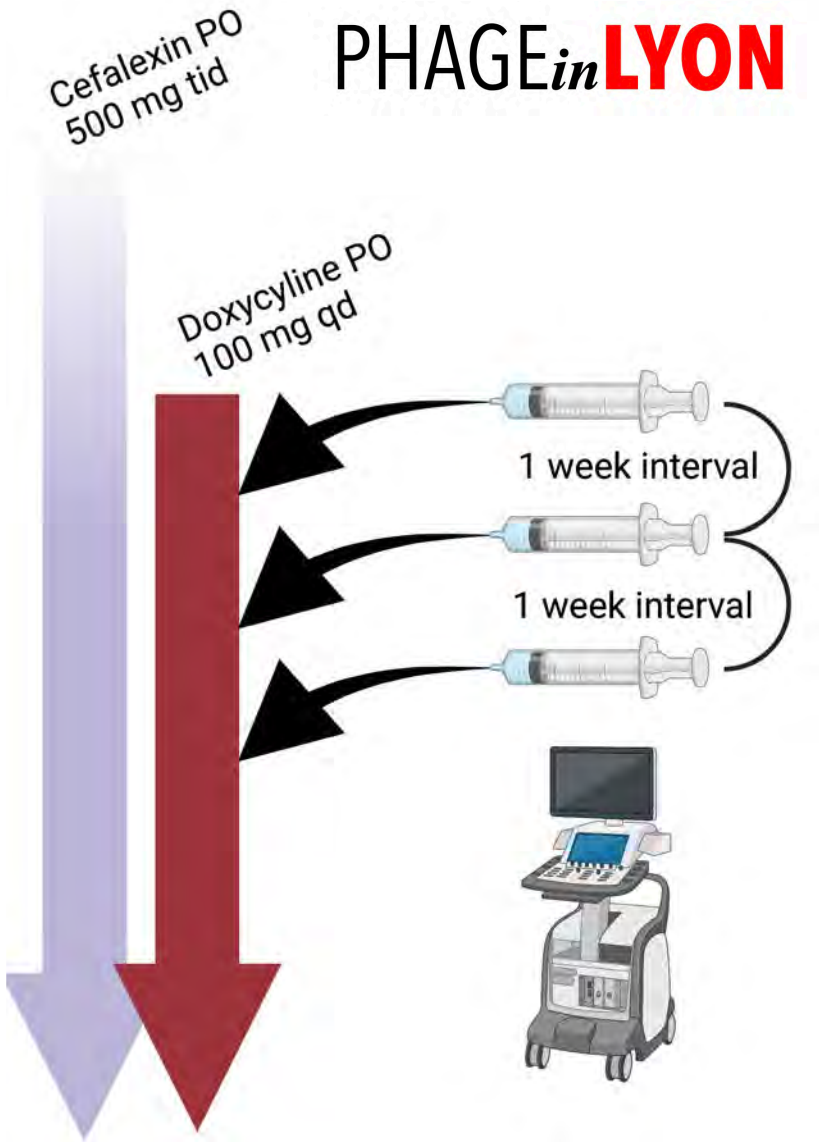
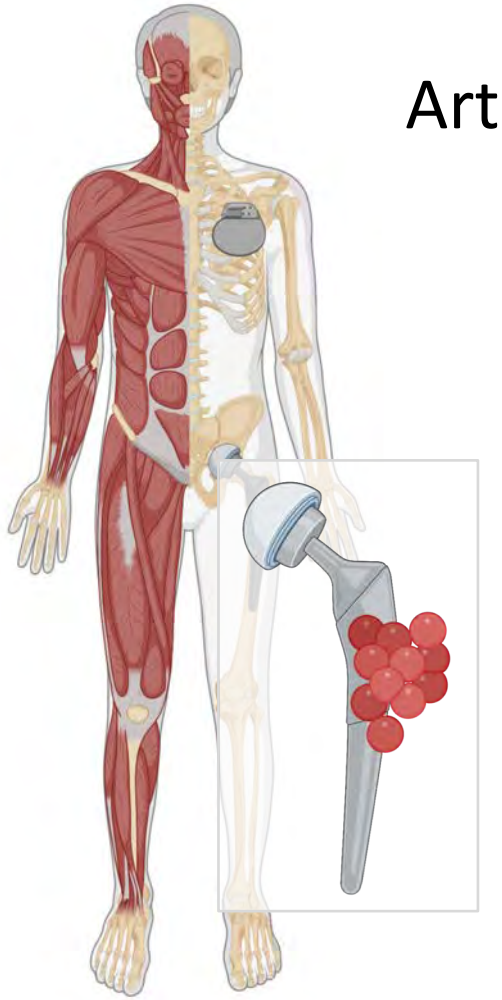


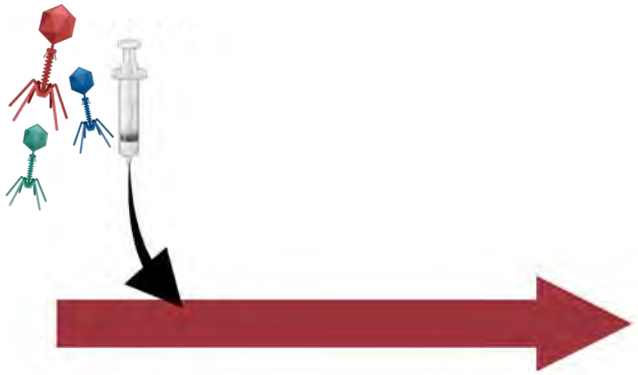
PHAGE *in* LYON

Clinic



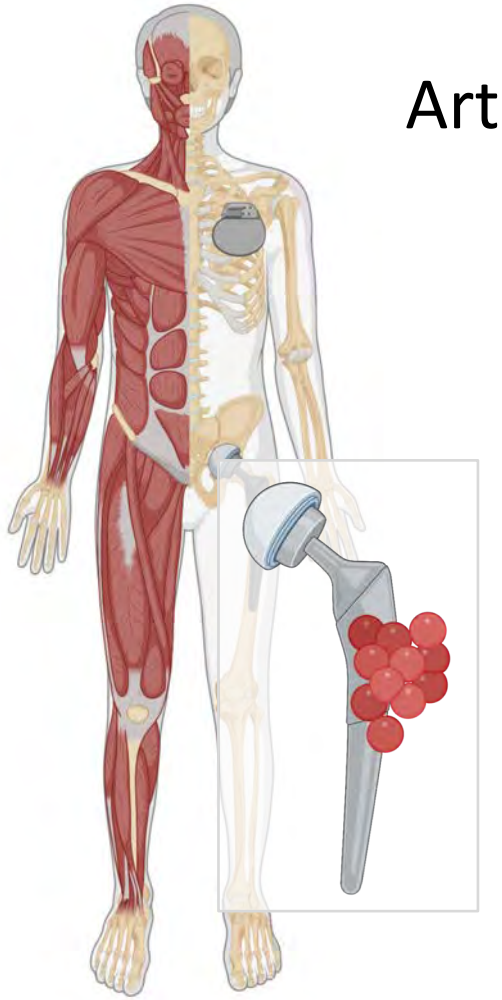
Arthroscopic or open

DAIR



PHAGE *in* LYON Clinic

*See FP E1 EBJIS 2022



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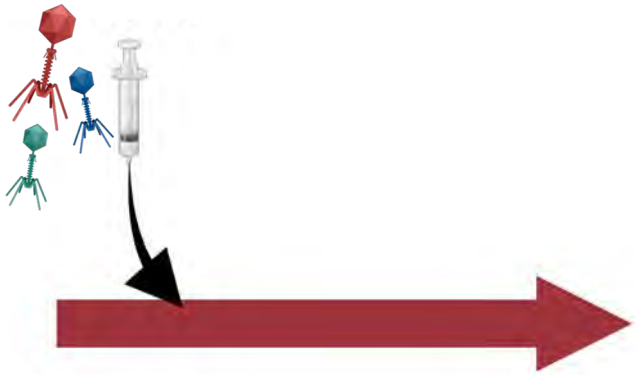
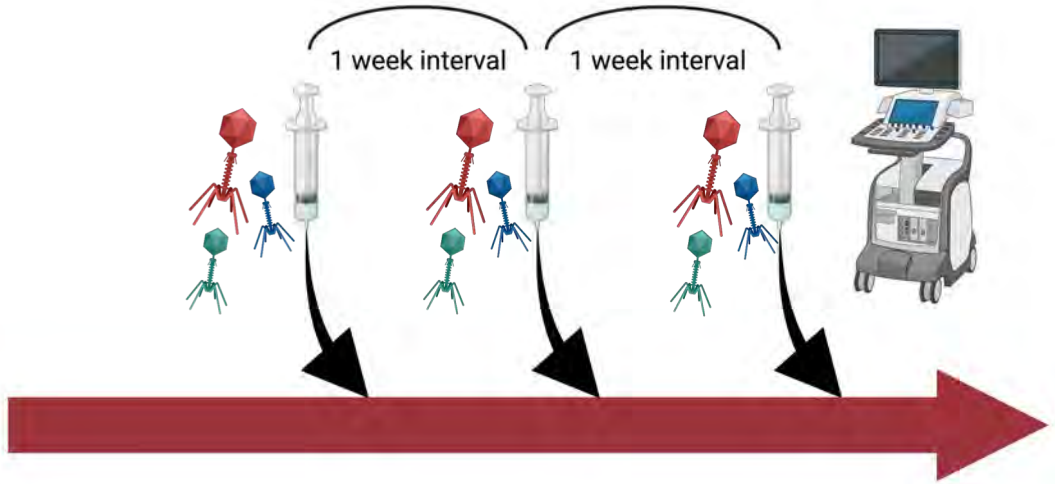
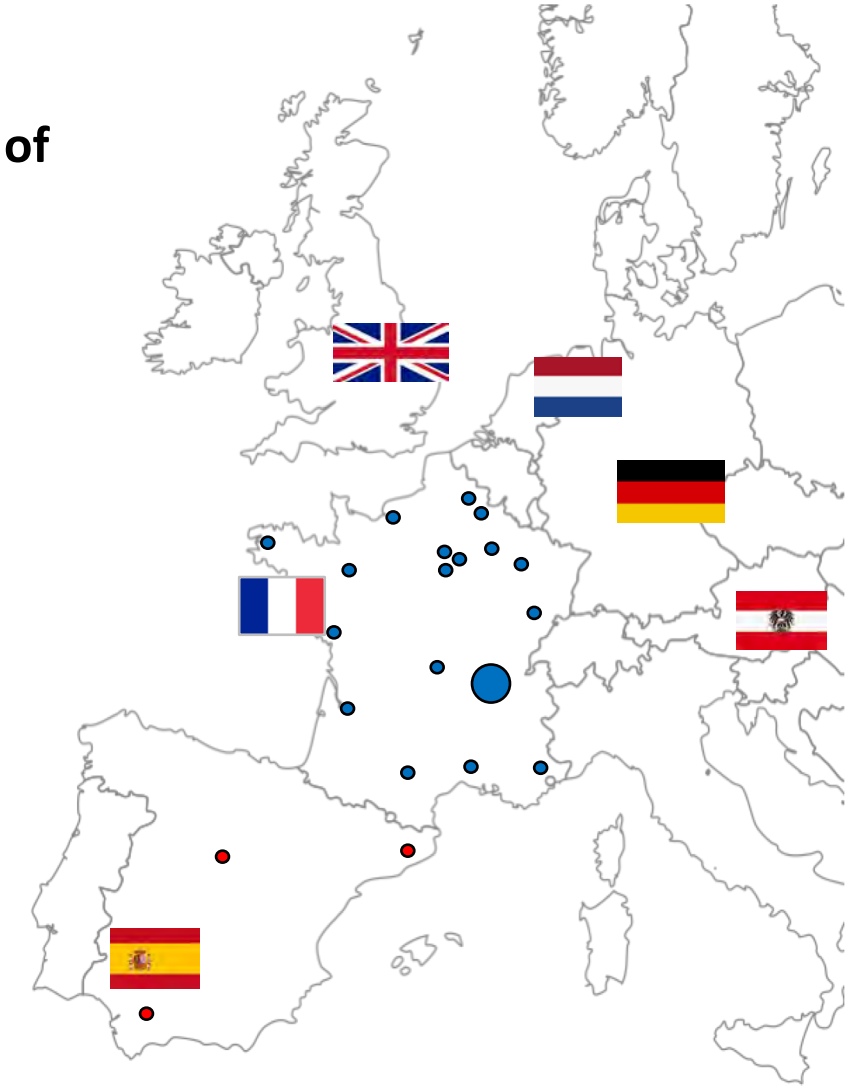


in case of **relapse**
OR **after DAIR** if no phages were available at the time of the DAIR*
OR if **no DAIR** could be performed



PhagoDAIR I

A Pilot, Multicenter, Randomized, Non-Comparative, Double-Blind Study of Phage Therapy in Patients with Hip or Knee PJI due to *S. aureus* Treated with DAIR and Antibiotic Therapy



Inclusion Criteria

1. ***S. aureus* monomicrobial** knee or hip **PJI** with clinical signs of infection with indication of **DAIR** and **Suppressive Antibiotics Therapy (SAT).**
2. Phagogram displaying the susceptibility of the strain to at least one of the anti-*Staphylococcus aureus* bacteriophages

Primary Objective

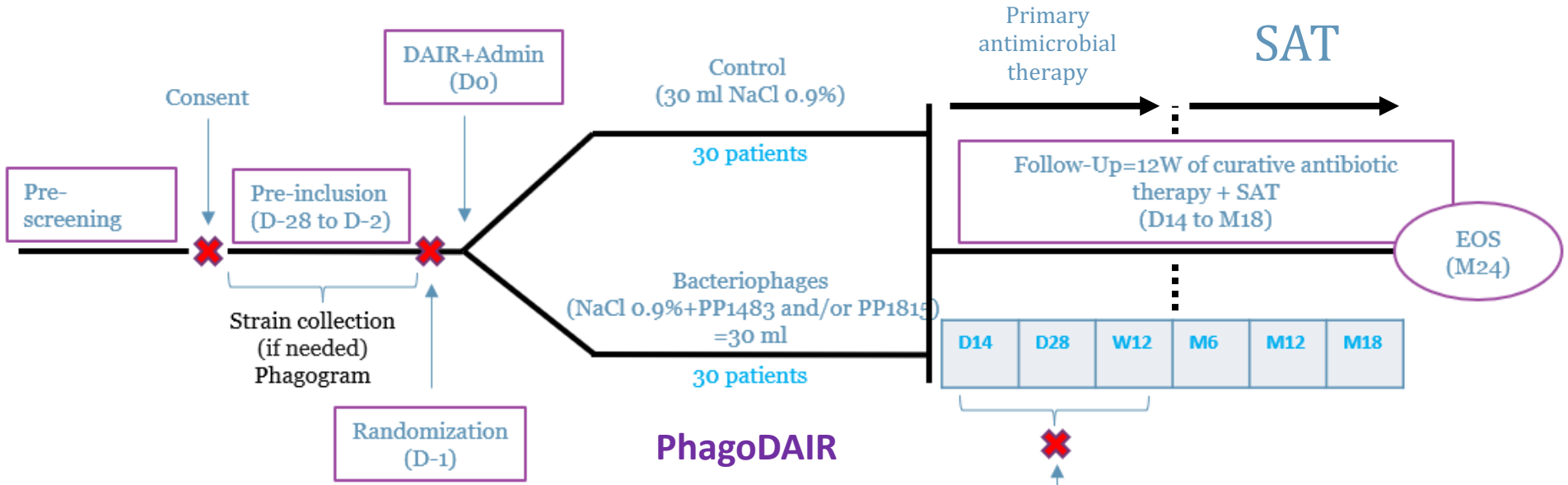
To estimate the **rate of clinical control of infection at Week 12±2** which will allow to calculate the sample size for future comparative studies.

PHERECYDES PHARMA

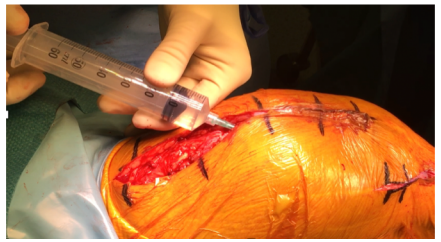
PhagoDAIR I

A Pilot, Multicenter, Randomized, Non-Comparative, Double-Blind Study of Phage Therapy in Patients with Hip or Knee PJI due to *S. aureus* Treated with DAIR and Antibiotic Therapy

Study design



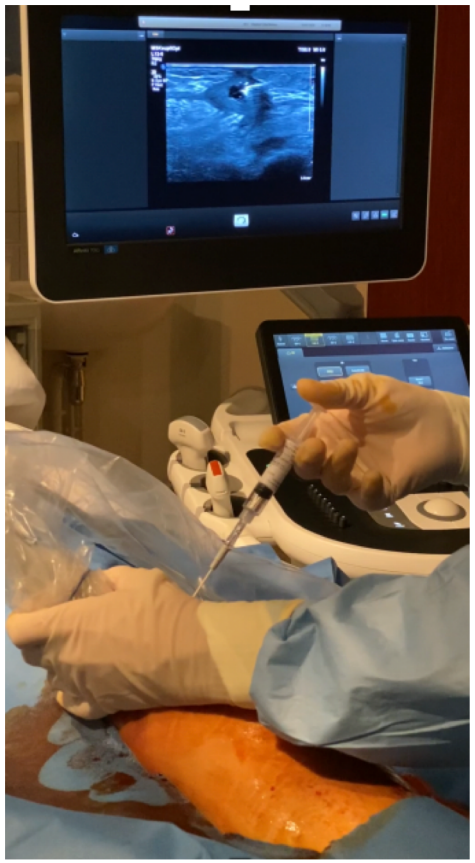
PhagoDAIR



Salvage procedure

- Pre-treatment (D-15 to D-1)
- Active phages admin at D0-RT, D7-RT, and D14-RT
- Follow-Up (D28-RT to M18)
- EOS at M24

Salvage procedure



Clinical case (3rd treated patient)

Arthroscopic DAIR with phages to salvage *P. aeruginosa* prosthetic knee infection

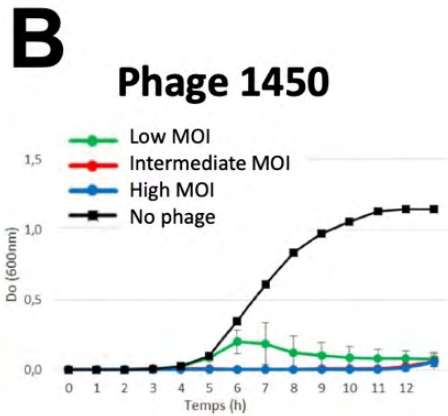
frontiers in Medicine 2021

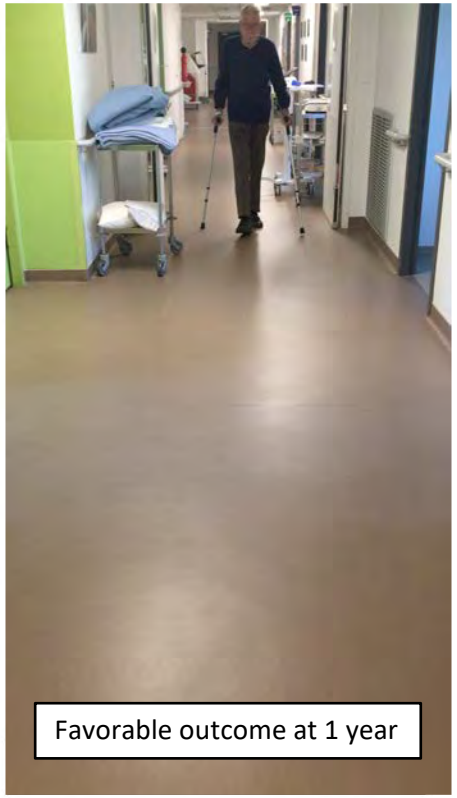
88-year-old man

Relapsing *P. aeruginosa* prosthetic left knee infection

End-stage cardiac failure

Contraindicated to open DAIR





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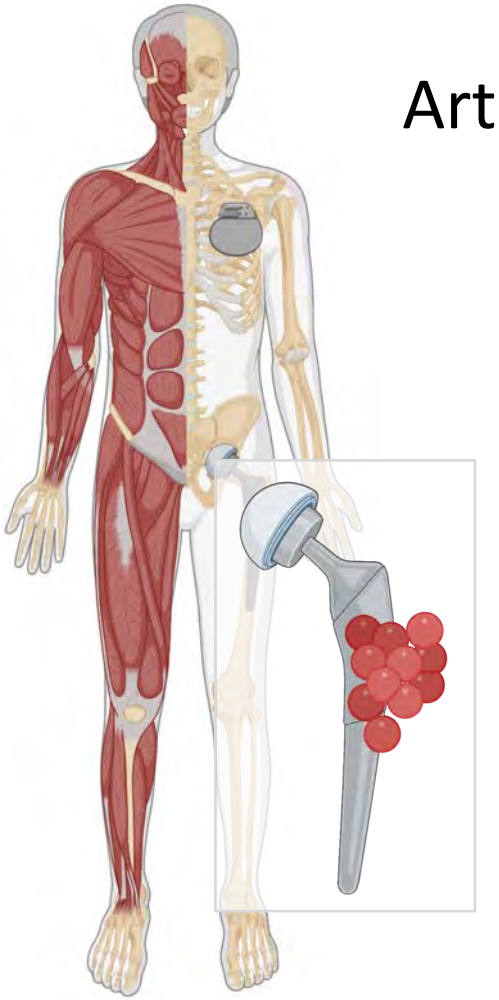
PHAGE *in* LYON Clinic



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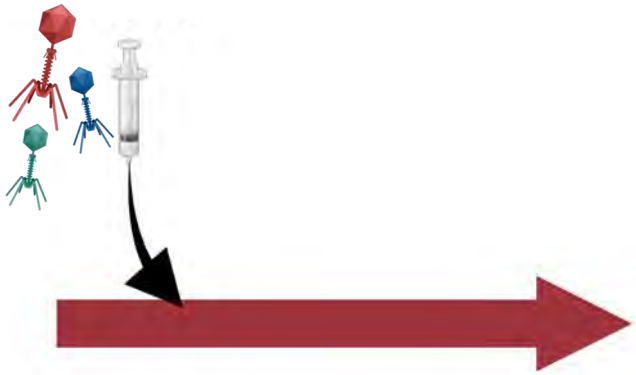
DAIR



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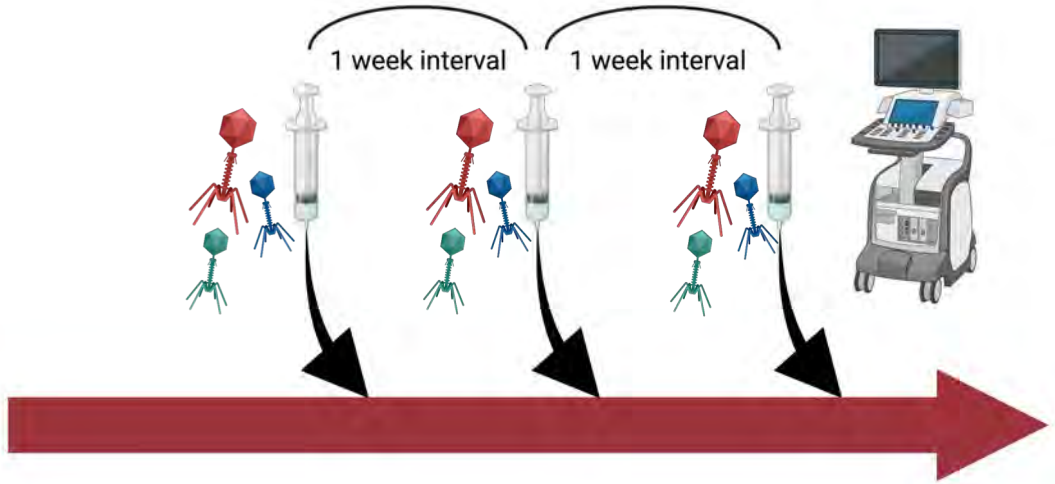
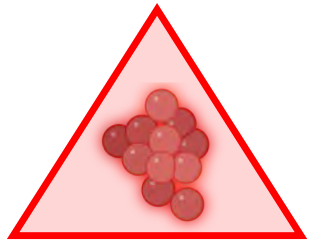


A large panel of **severe** bacterial infections



Central nervous system infections

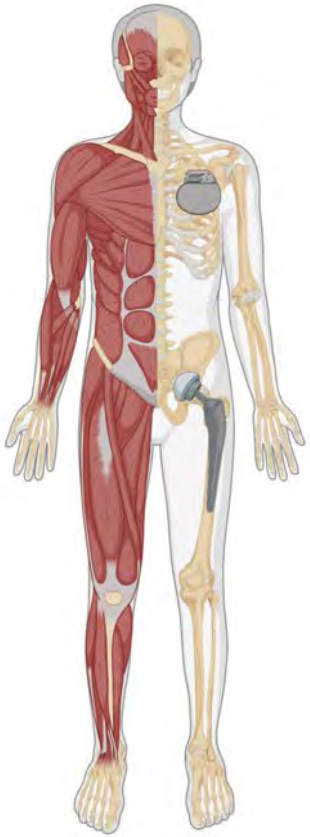
Implant-associated meningitis

Lung infections

Ventilator-associated pneumonia
Exacerbation in cystic fibrosis
Exacerbations in bronchiectasis

Urinary tract infections

Pyelonephritis
Ureteral stent-associated infection



Cardiovascular infections

Endocarditis
Cardiac electronic device infection
Prosthetic-valve endocarditis
Vascular graft infection

Muskuloskeletal infections

Wound infection
Osteomyelitis, fracture-related infection
Implant-associated bone and joint infection
Prosthetic joint infection

Digestive-tract infection

Typhoid fever, shigellosis
Cholera

Clinical case

62-year-old woman

Leiomyosarcoma

Radiotherapy

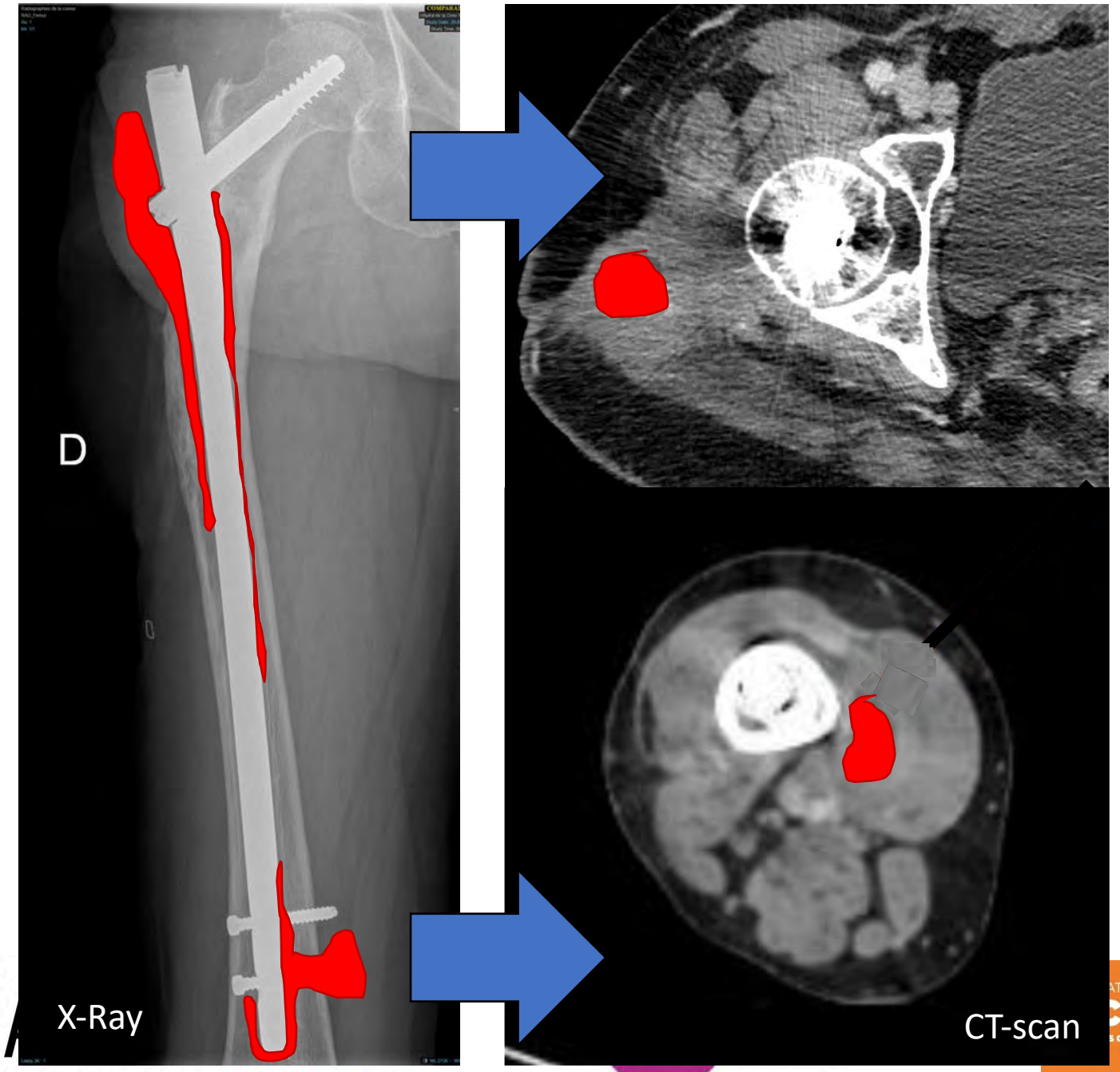
Fracture

Osteosynthesis, soft tissue flap

2-stage exchange of a nail

<u>Recurrent *S. aureus* infection</u>

Proximal and distal **<u>abscesses</u>**



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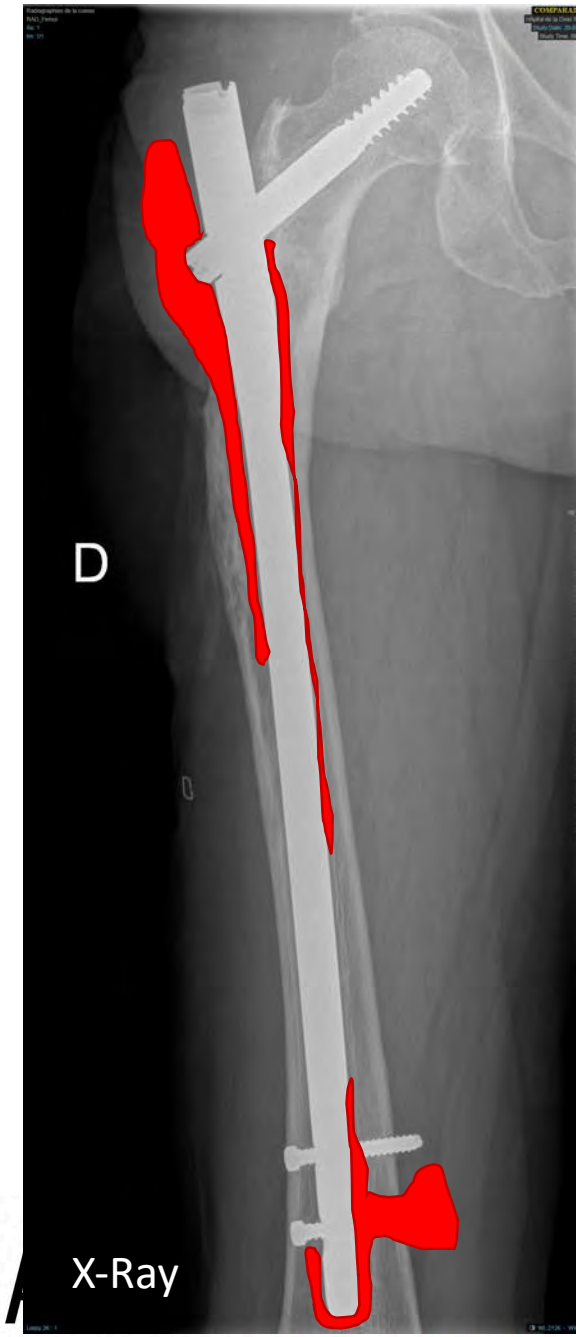


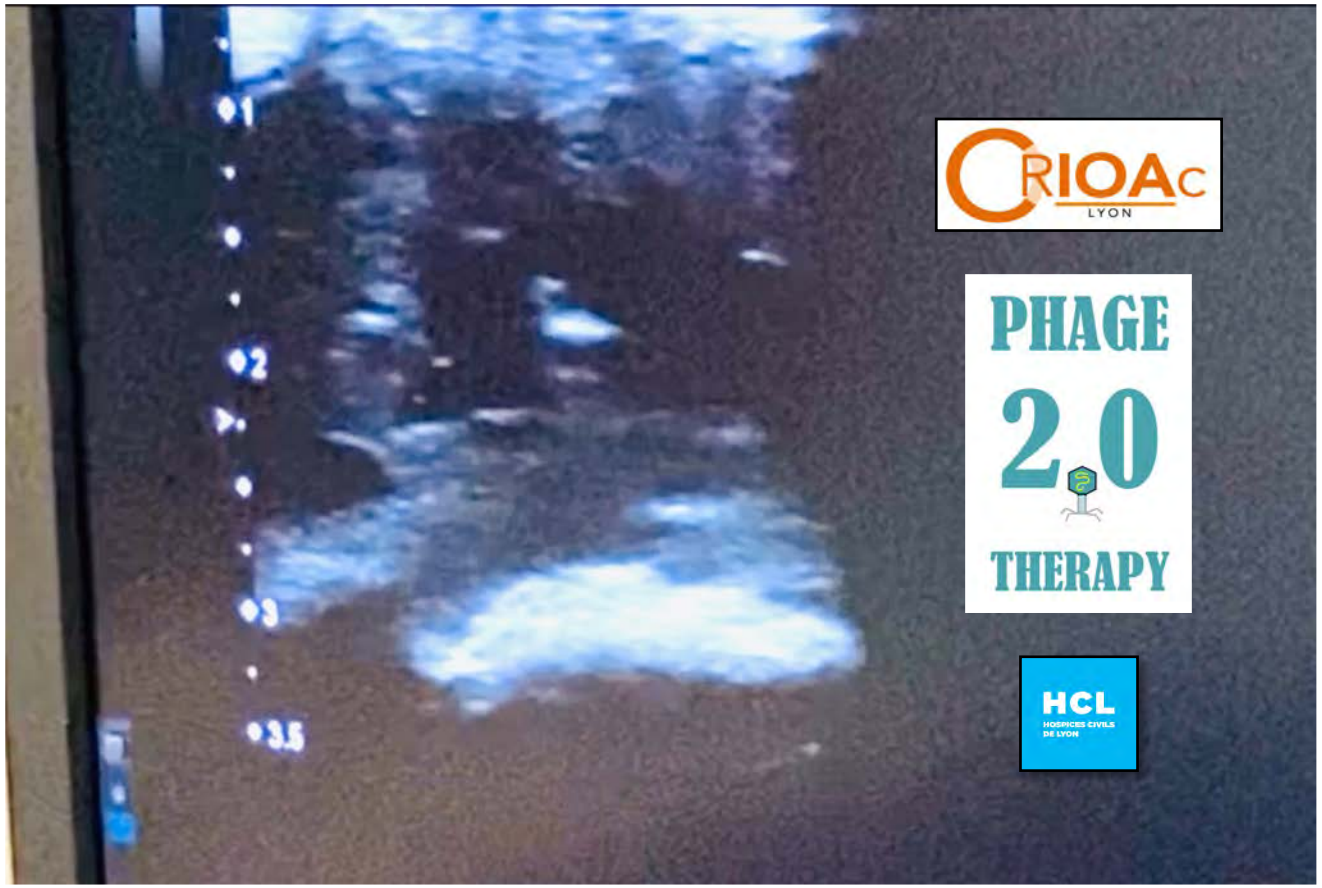
X-Ray

Clinical case

No surgery

Personalized **phage cocktail**

One shot phage injection



Highly purified phage cocktail 10^9 phages/mL

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Clinical case

No surgery

Personalized **phage cocktail**

One shot phage injection

Primary then suppressive antimicrobial therapy (cephalexin)

Favorable outcome at 18 months

Clinical case

No surgery

Personalized **phage cocktail**

One shot phage injection

Primary then suppressive antimicrobial therapy (cephalexin)

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Clinical case

No surgery

Personalized **phage cocktail**

One shot phage injection

Primary then suppressive antimicrobial therapy (cephalexin)

Favorable outcome at 18 months

"I acknowledge so much Pr. Ferry and the PHAGE*in*LYON *Clinic team, thanks to them, I save precious time!"*

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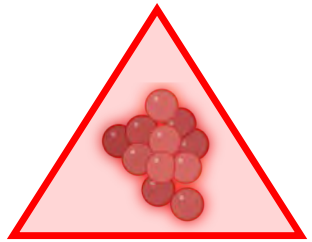

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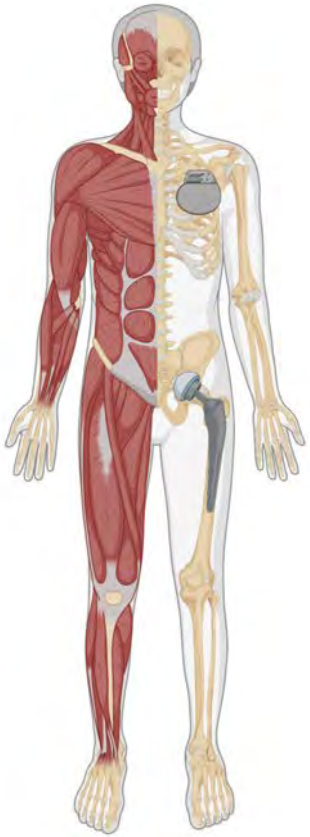

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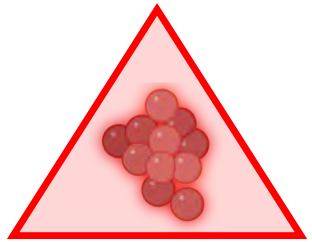

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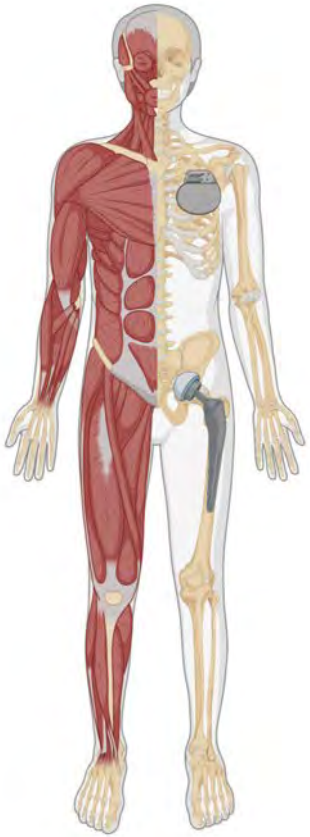

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Clinical cases (not published)

Patient de 49 ans
Valve biologique tricuspide avec **infection récidivante**
Chirurgie itérative, **endocardite récidivante** à ***P. aeruginosa***
Phagothérapie IV selon les modalités définies aux HCL en 2021
Préparation et dilution d'un **cocktail actif** (Pherecydes Pharma)

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Préparation et dilution d'un **cocktail actif** (Pherecydes Pharma)

Négativation des hémocultures
Traitement suppressif par ciprofloxacine (arrêté rapidement)
Pas de récidive à 2 ans (hémocultures systématiques)

Clinical cases (not published)

Phagothérapie envisageable

Patients en échec

Récusés chirurgicalement

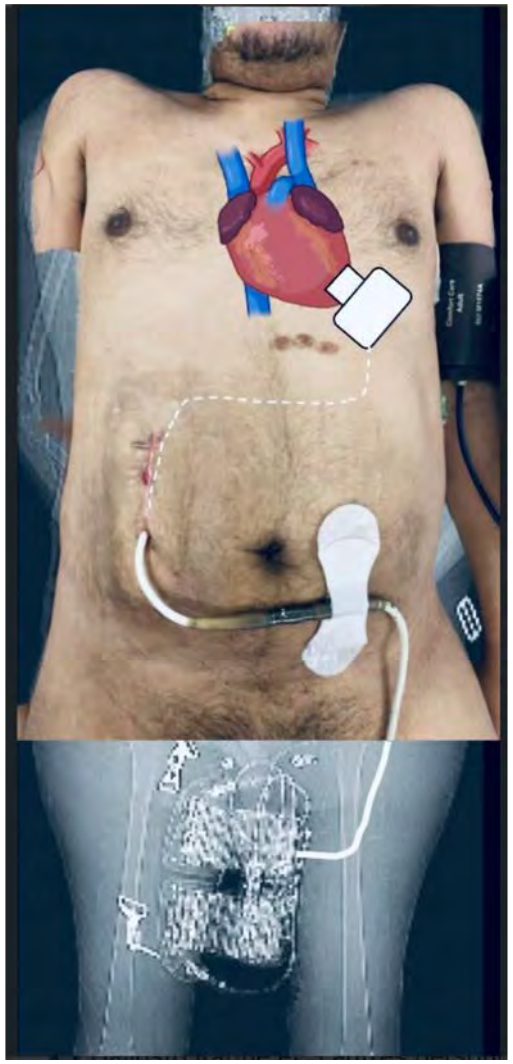
Personnalisation et hiérarchisation des modalités d'administration

RCP Phagothérapie HCL

Intraveineux exclusif (1 injection/j pendant 7 jours)

A confirmer par un essai thérapeutique

HeartMate 3



Jarvik 2000

Berlin Heart

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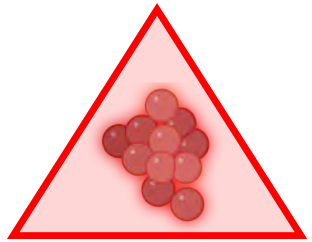

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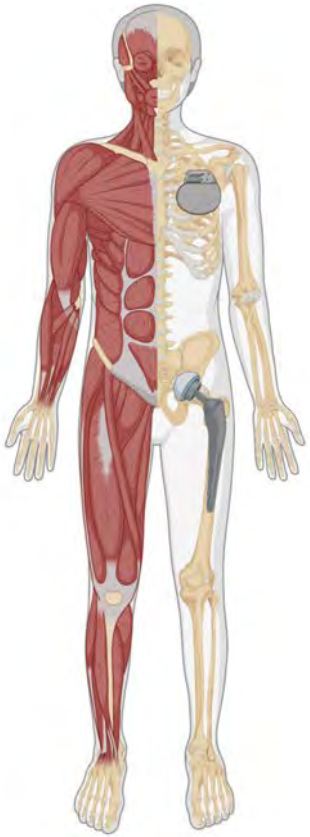

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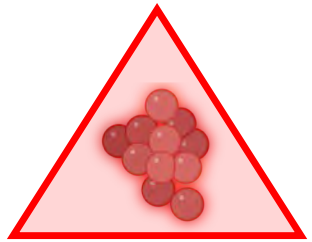

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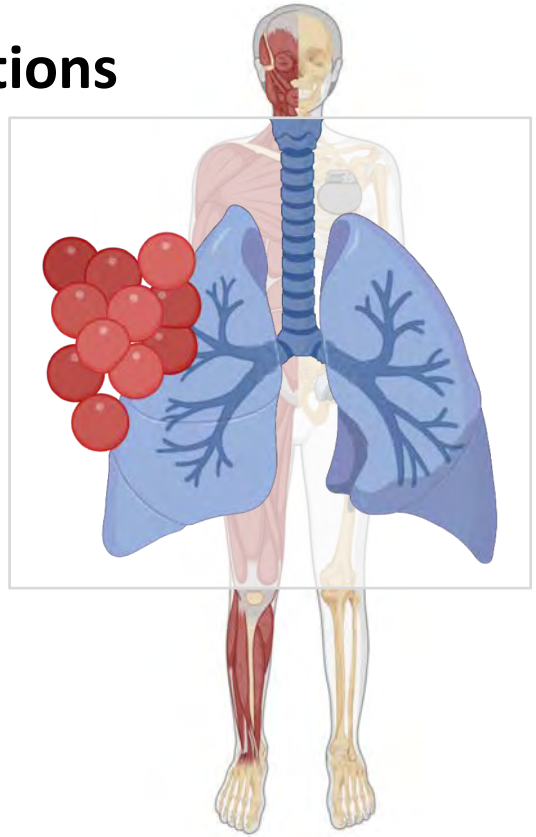

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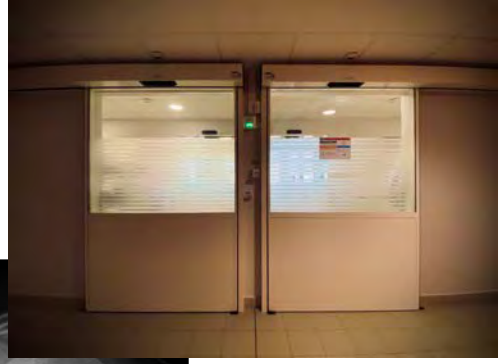

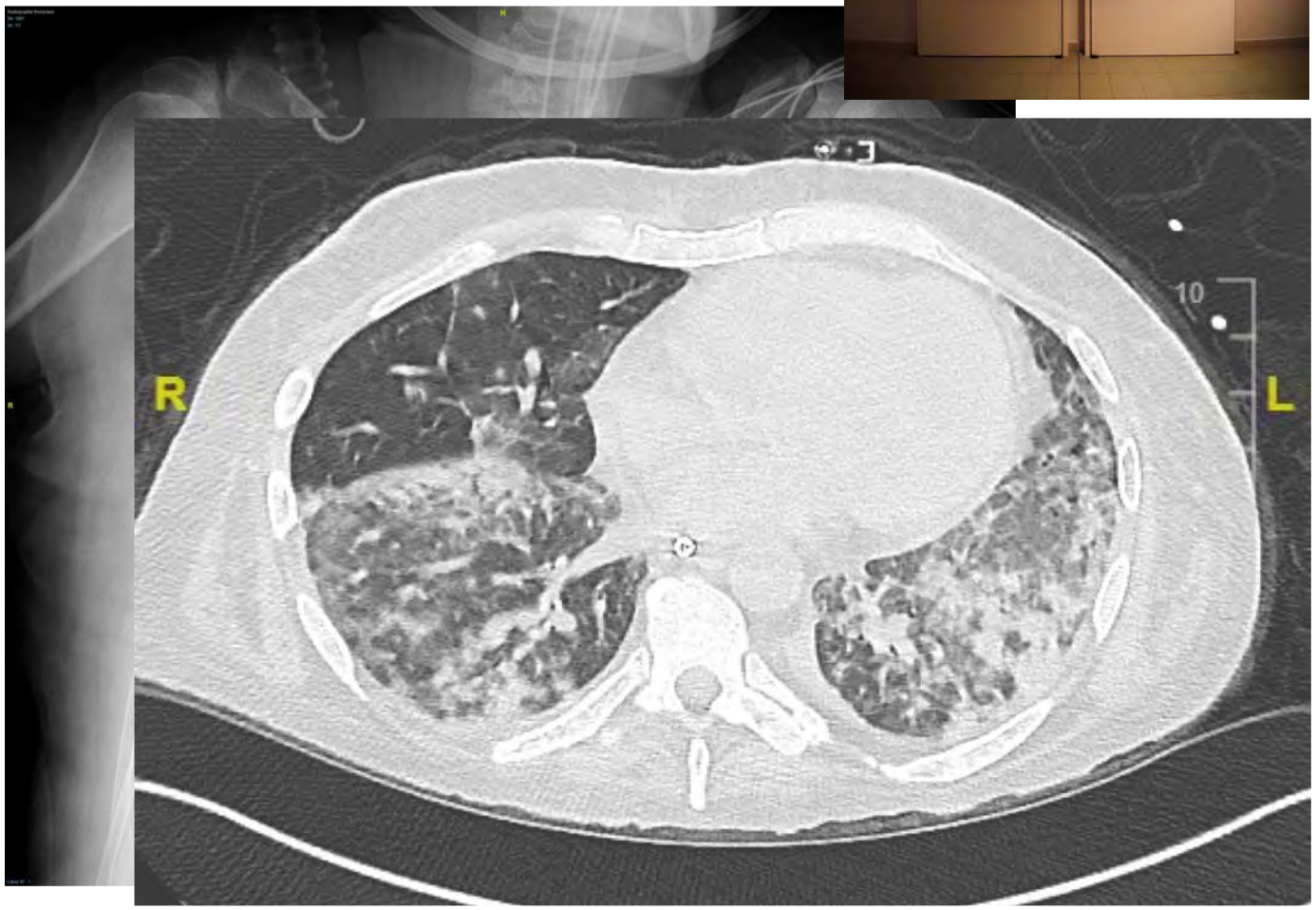

52-year-old man

Burn (81% of the body surface)

In ICU

Ventilator-associated pneumonia

Pandrug-resistant *P. aeruginosa*

Treated with imipenem-relebactam

Relapsing VAP with bacteremia

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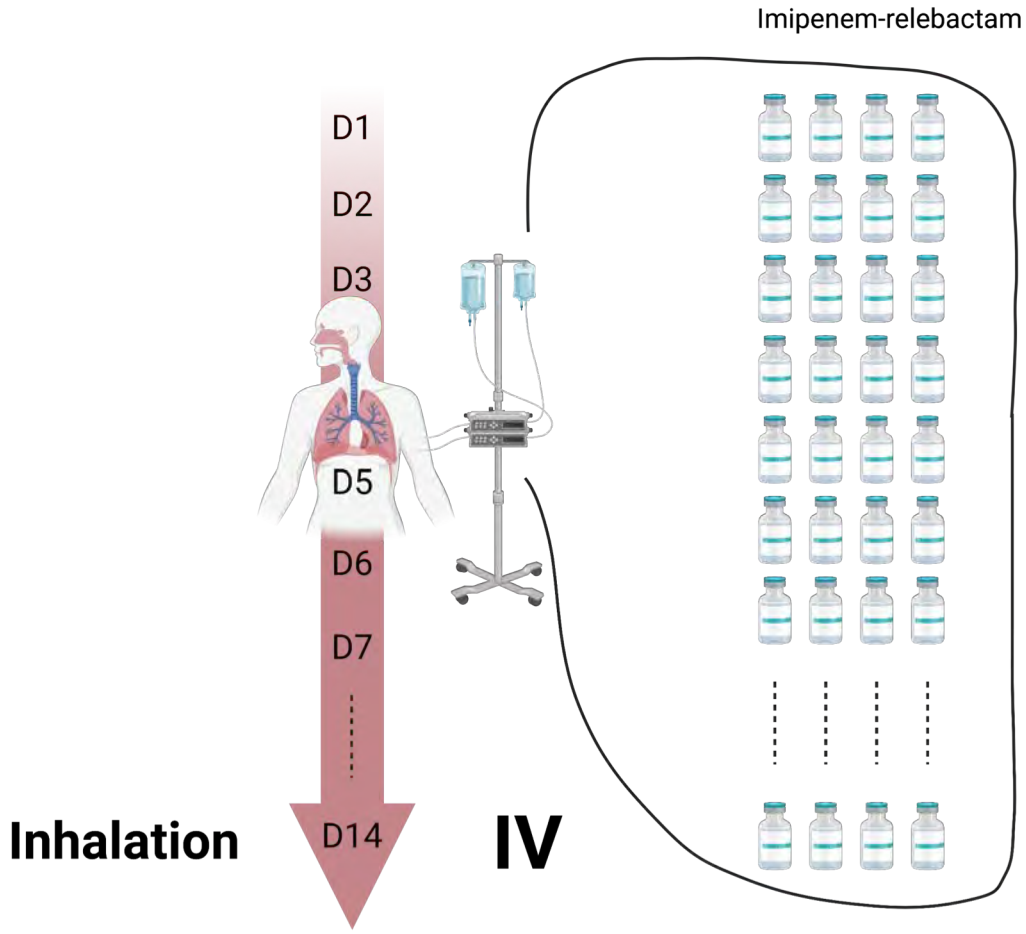

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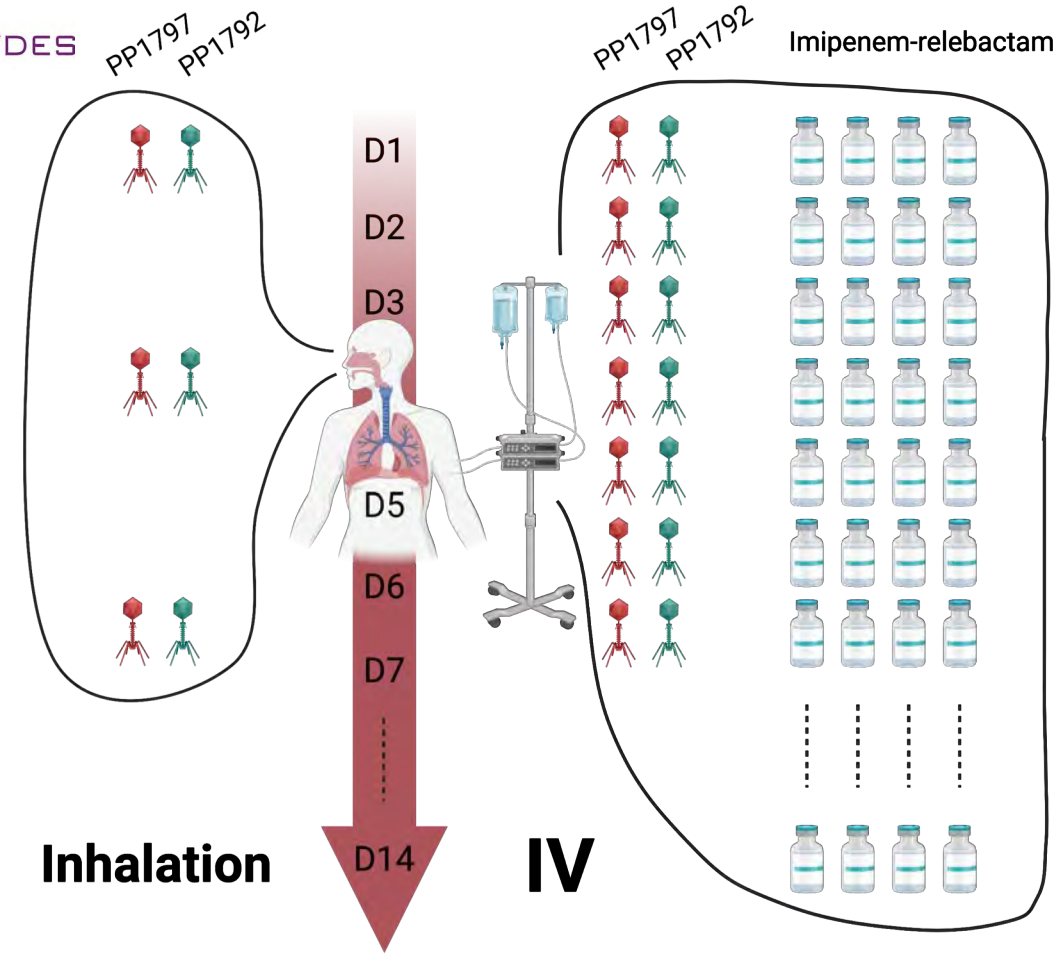
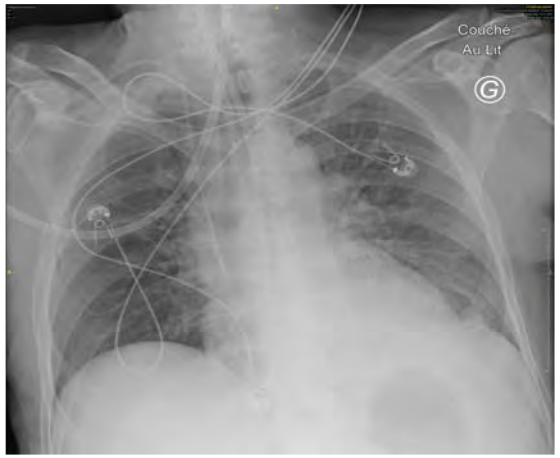


Vibrating Mesh nebuliser



Courtesy O. Martin

HCL HOSPICES CIVILS DE LYON

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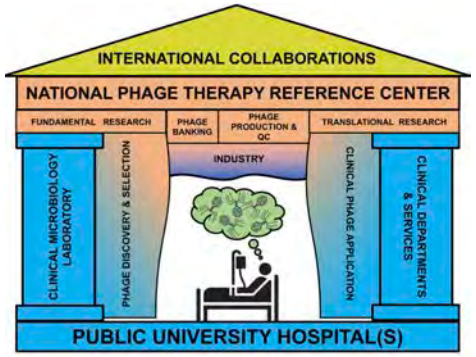

Phage therapy center

+

CRIOAc LYON

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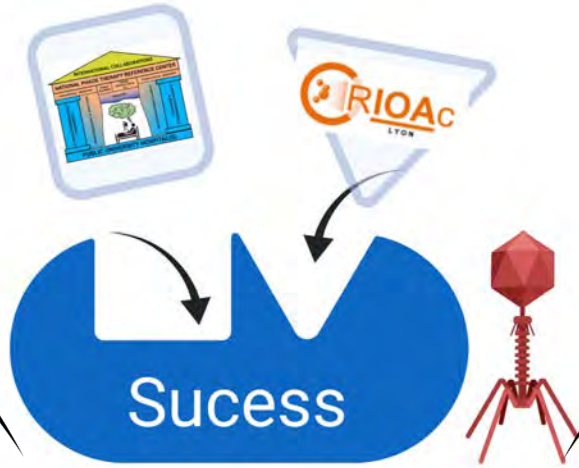
Referral center complex BJI

Phages from the industry
Phages from academic
Lysins from the industry

Dedicated referral activity
Significant number of patients
Relevant clinical situations



Significant level of Scientific evidence

Disruptive approach

Individual patient benefit

Compassionate use indication
Multidisciplinar meetings
Phage therapy

In June 2023 (T. Ferry)

HCL HOSPICES CIVILS DE LYON

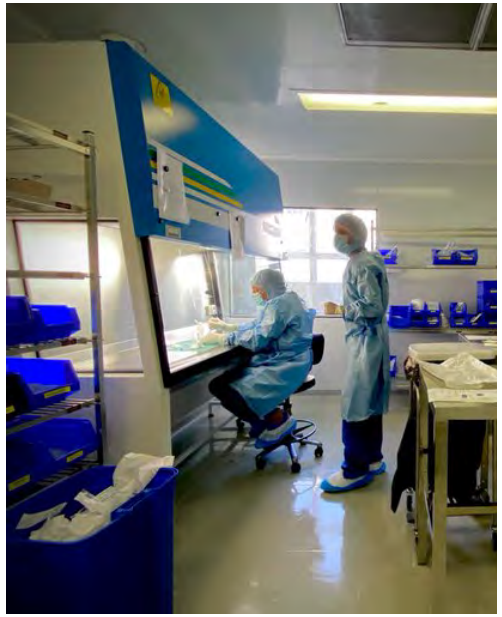
FONDATION HCL HOSPICES CIVILS DE LYON

Indication of phage therapy
Ways of administration
French health autorities

PHAGE*in*LYON Clinic

Phagogram

PHERECYDES PHARMA



Cohort Study
PHA-SA-CO
Phage Safety
Cohort Study
(biobanking)

FONDATION HCL HOSPICES CIVILS DE LYON

Compassionate use indication
Multidisciplinar meetings
Phage therapy

In June 2023 (T. Ferry)

MHKA
HMRA

taiΦr
Tailored Antimicrobials and Innovative Laboratories for Phage (Φ) Research

HCL HOSPICES CIVILS DE LYON

ESGNTA ESCMID STUDY GROUP FOR NON-TRADITIONAL ANTIBACTERIAL THERAPY
European Society of Clinical Microbio

HCL HOSPICES CIVILS DE LYON

FONDATION HCL HOSPICES CIVILS DE LYON

Indication of phage therapy
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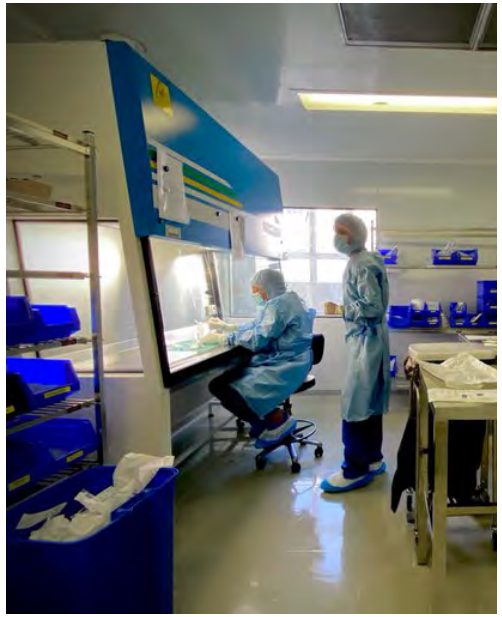
Phagogram

PHERECYDES PHARMA

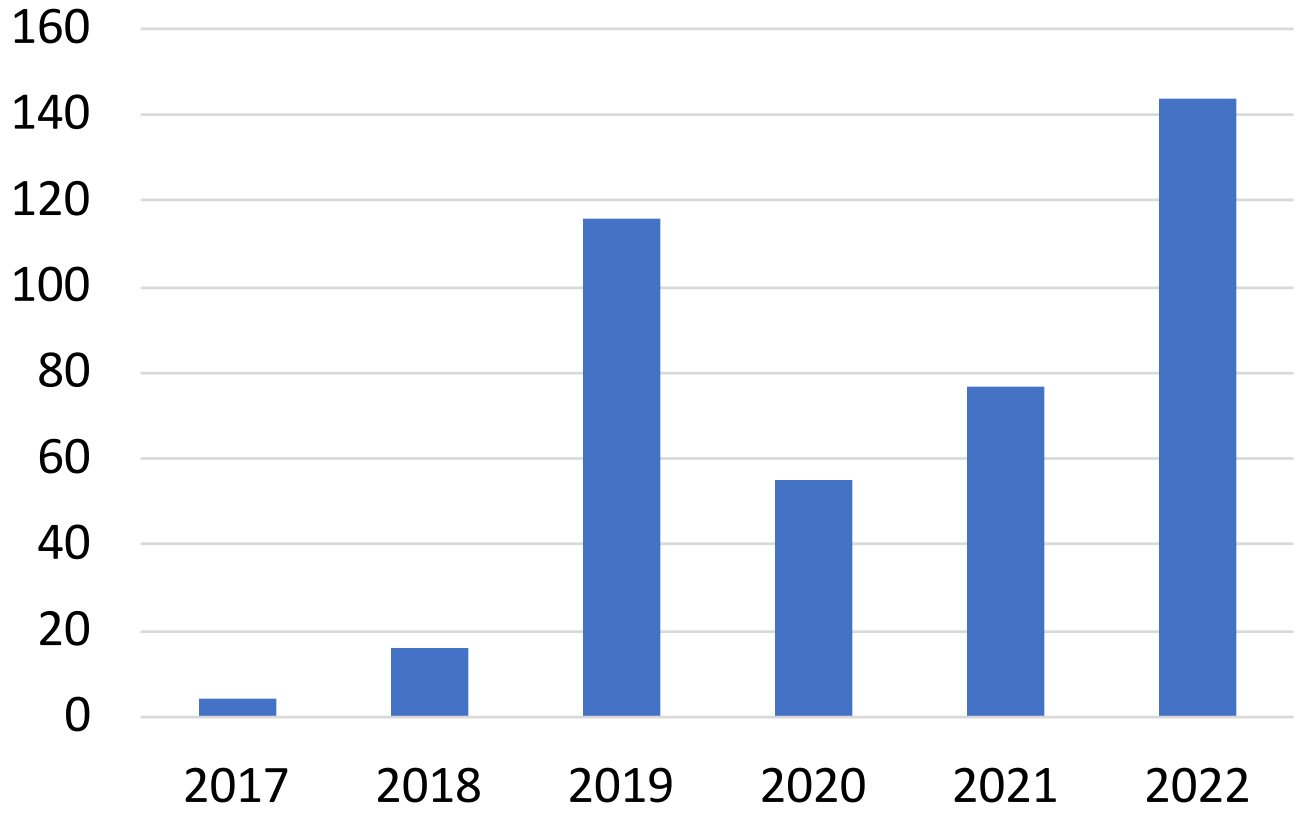
PHAGE*in*LYON *Clinic*



Cohort Study
PHA-SA-CO
Phage Safety
Cohort Study
(biobanking)

FONDATION HCL HOSPICES CIVILS DE LYON

Phage requests



PHAGE*in*LYON *Clinic*

Involved bacteria

32 % *Staphylococcus aureus*

16 % *Pseudomonas aeruginosa*

6 % *Staphylococcus epidermidis*

Type of infction

37% Prosthetic-joint infection

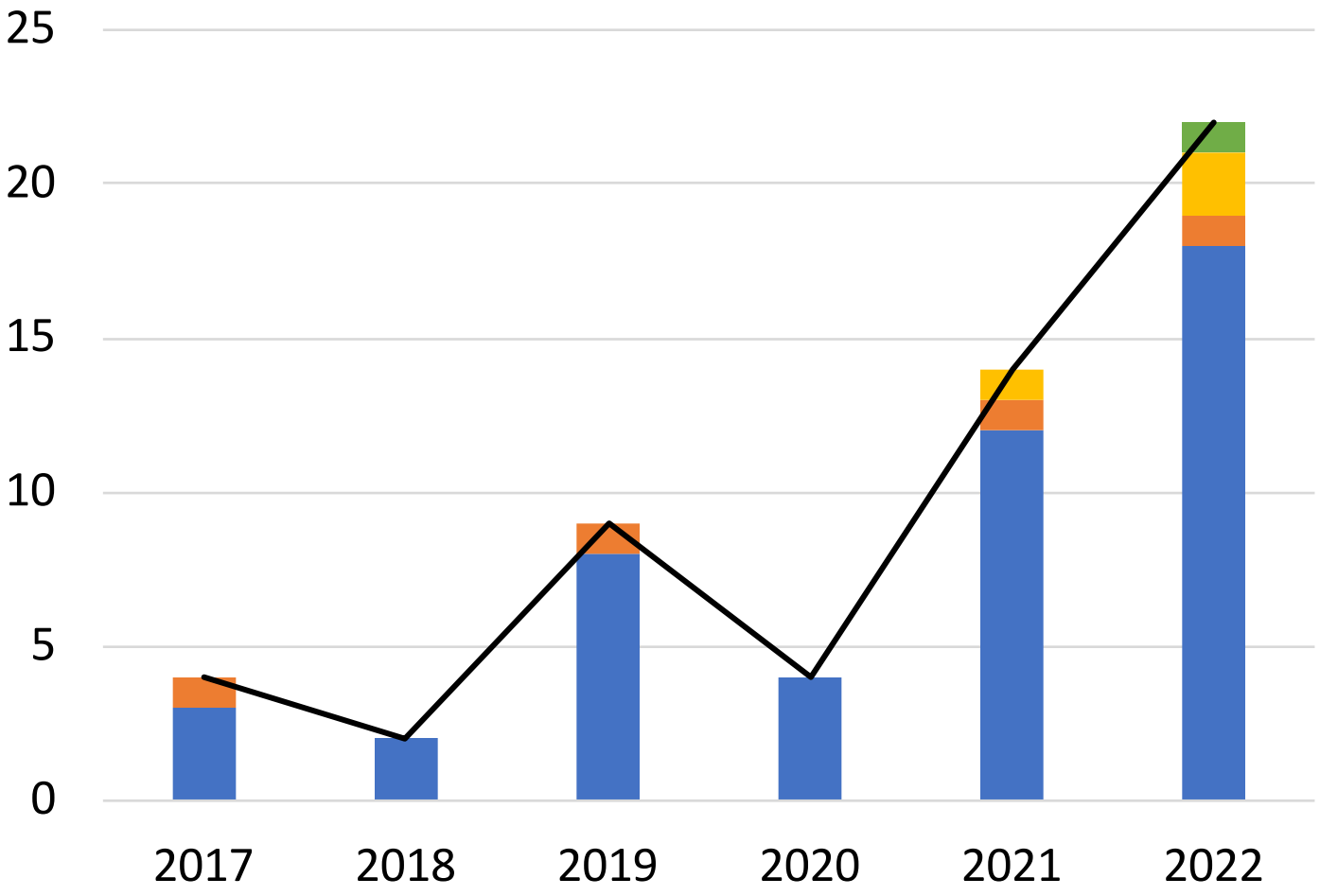
27% Other bone and joint infection

8% Lung infection

Source : T. Ferry

Treated patients

PHAGE*in*LYON Clinic



- Bone and joint
- Endocarditis
- Other
- Lung
- Vascular graft infection

Source : T. Ferry

Lyon 1 · RIOAc LYON · ciri Centre International de Recherche en Infectiologie · Fondation HCL Hospices Civils de Lyon · HCL Hospices Civils de Lyon

The pyramid of bacterial infectious diseases

life- or limb- threatening infections

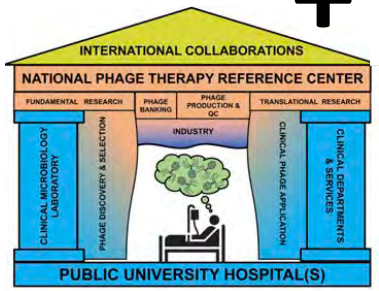
Relapsing severe bacterial infections

Severe bacterial infections

Nonsevere bacterial infections

Frequency

+



RIOAc LYON

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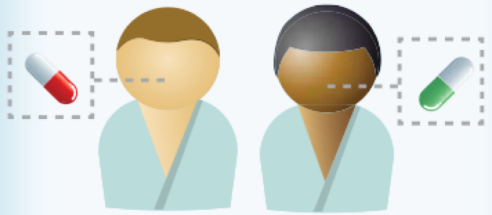
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical trials

U.S. Food and Drug Administration
FDA **Drug Approval Process**



Phase 1 (n ≈ 20-80)
Phase 2 (n ≈ 100)
Phase 3 (n ≈ 1000)

Clinical case (12th treated patient)

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!

Clinical case (12th treated patient)

74-year-old man

Melanoma treated with anti-PD1

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

Spinal pain summer 2018

Spondylodiscitis with **spina**

Pandrug-resist

	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)
[illegible]xacine	R (> 4)
[illegible]oxazole	R
[illegible]e	S (8) ⇨ R
	S E-test : 1 ⇨ R
	R E-test : > 256
	R E-test : 64

PHERECYDES PHARMA

AMPLIPHI BIOSCIENCES CORPORATION

The strain was also spontaneously resistant to bacteriophages !!!

HCL HOSPICES CIVILS DE LYON

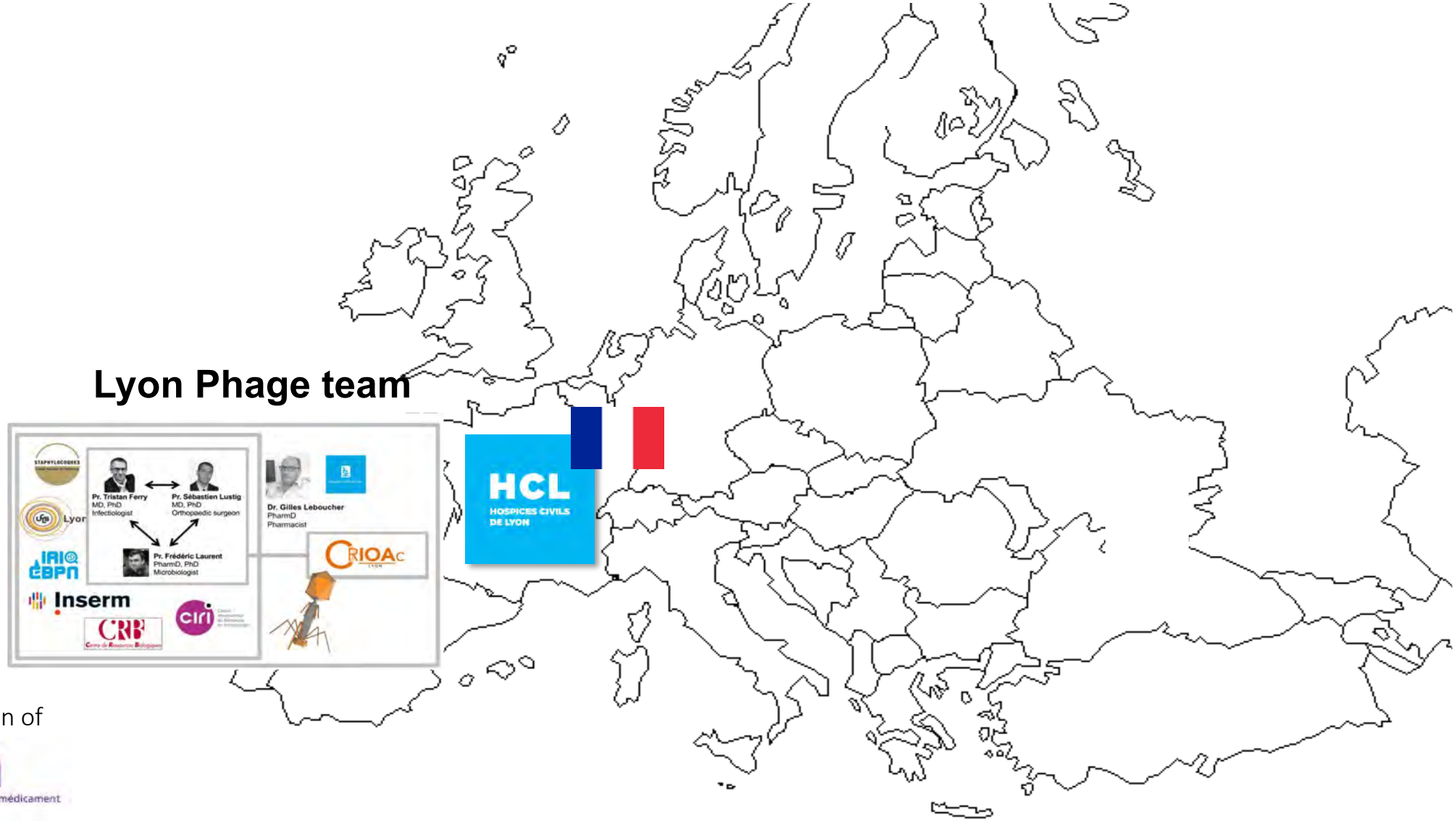
Lyon 1

PHAGE*in*LYON

ciri Centre International de Recherche en Infectiologie

FONDATION HCL HOSPICES CIVILS DE LYON

Unique European academic collaboration

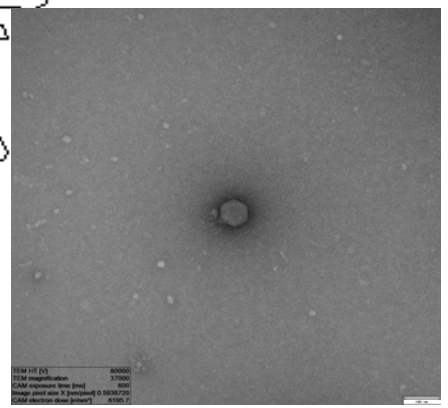


Under the supervision of

ansm
Agence nationale de sécurité du médicament et des produits de santé

French Health Authority

Unique European academic collaboration



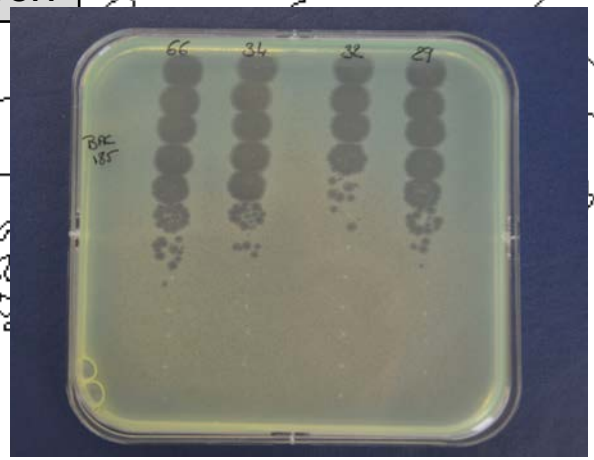
Jean-Paul Pirnay

Gregory Resch

Lyon Phage tea

HCL HOSPICES CIVILS DE LYON

UNIL | Université de



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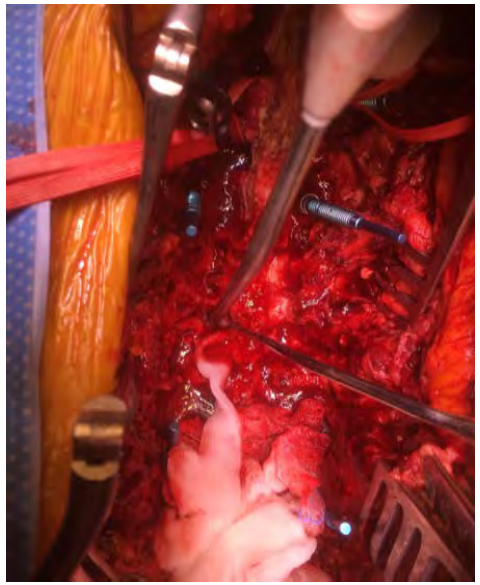

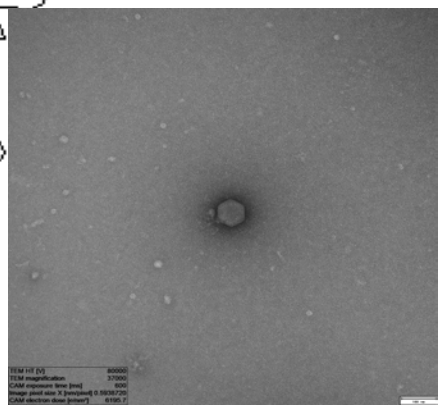

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HCL HOSPICES CIVILS DE LYON

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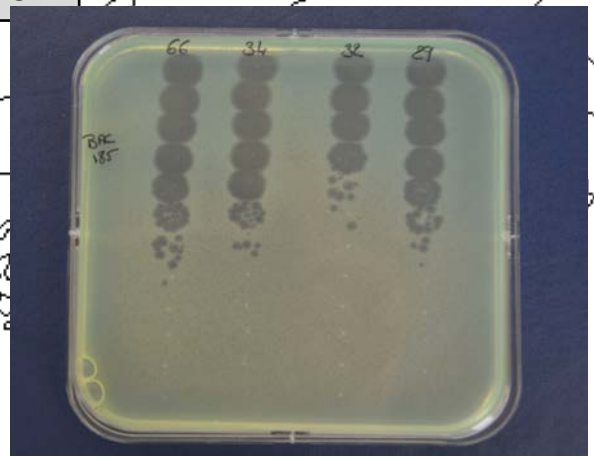

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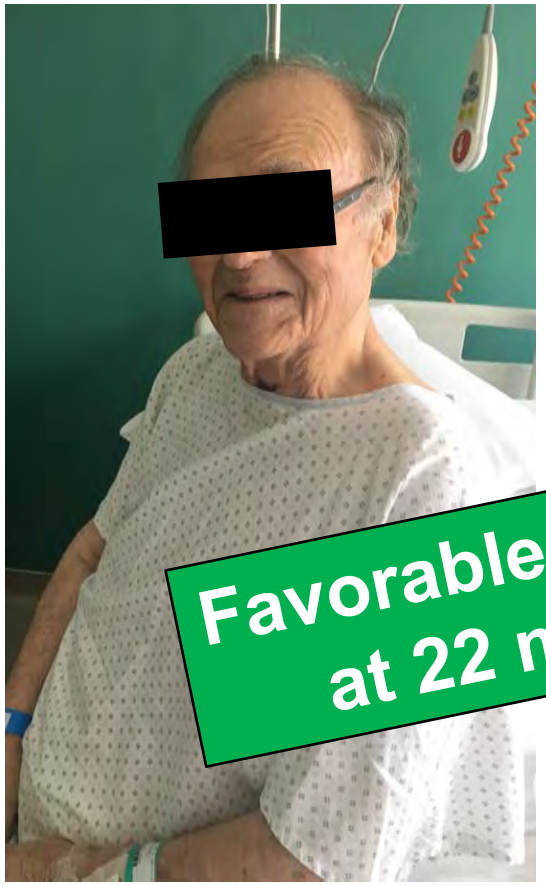
MHKA HMRA

UNIL | Université de Lausanne



Favorable outcome at 22 months

nature COMMUNICATIONS

T. FERRY et al. 2022

HCL PHAGE*in*LYON FONDATION HCL

Lyon 1 CRIOAc ciri

Under the supervision of

ansm Agence nationale de sécurité du médicament et des produits de santé

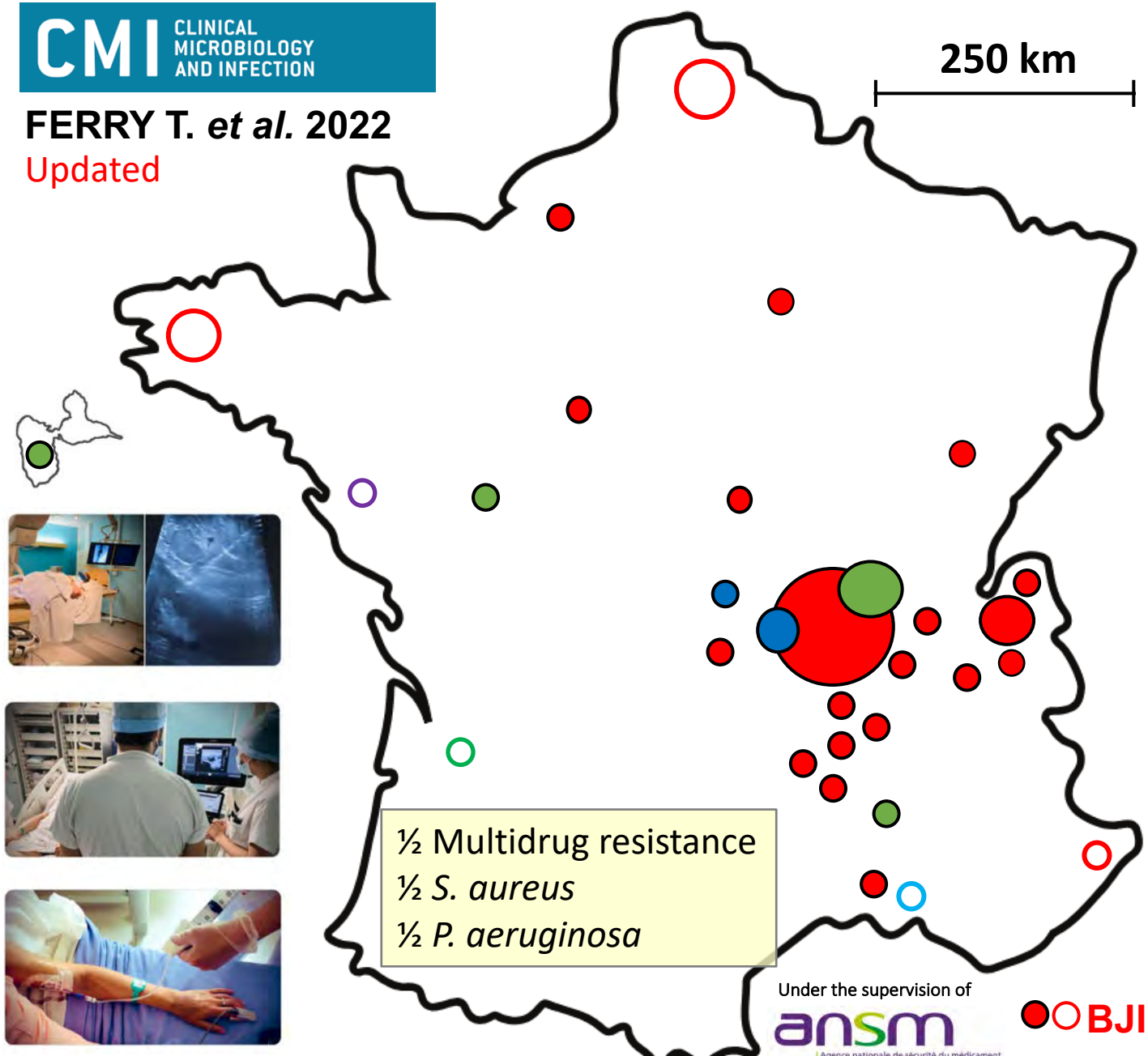
French Health Authority

Conclusions: Personalized phage therapy is a potential adjuvant 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.**

Implementation of a **Phage Therapy Center** in a CRIOAc

CMI CLINICAL MICROBIOLOGY AND INFECTION

FERRY T. *et al.* 2022
Updated



½ Multidrug resistance
½ *S. aureus*
½ *P. aeruginosa*

Under the supervision of ansm

HCL HOSPICES CIVILS DE LYON

PHAGE*in*LYON

FONDATION HCL HOSPICES CIVILS DE LYON

Lyon 1 · CRIOAc LYON · ciri Centre International de Recherche en Infectiologie

53 patients in Lyon since 2017
~80% of the whole patients treated in France

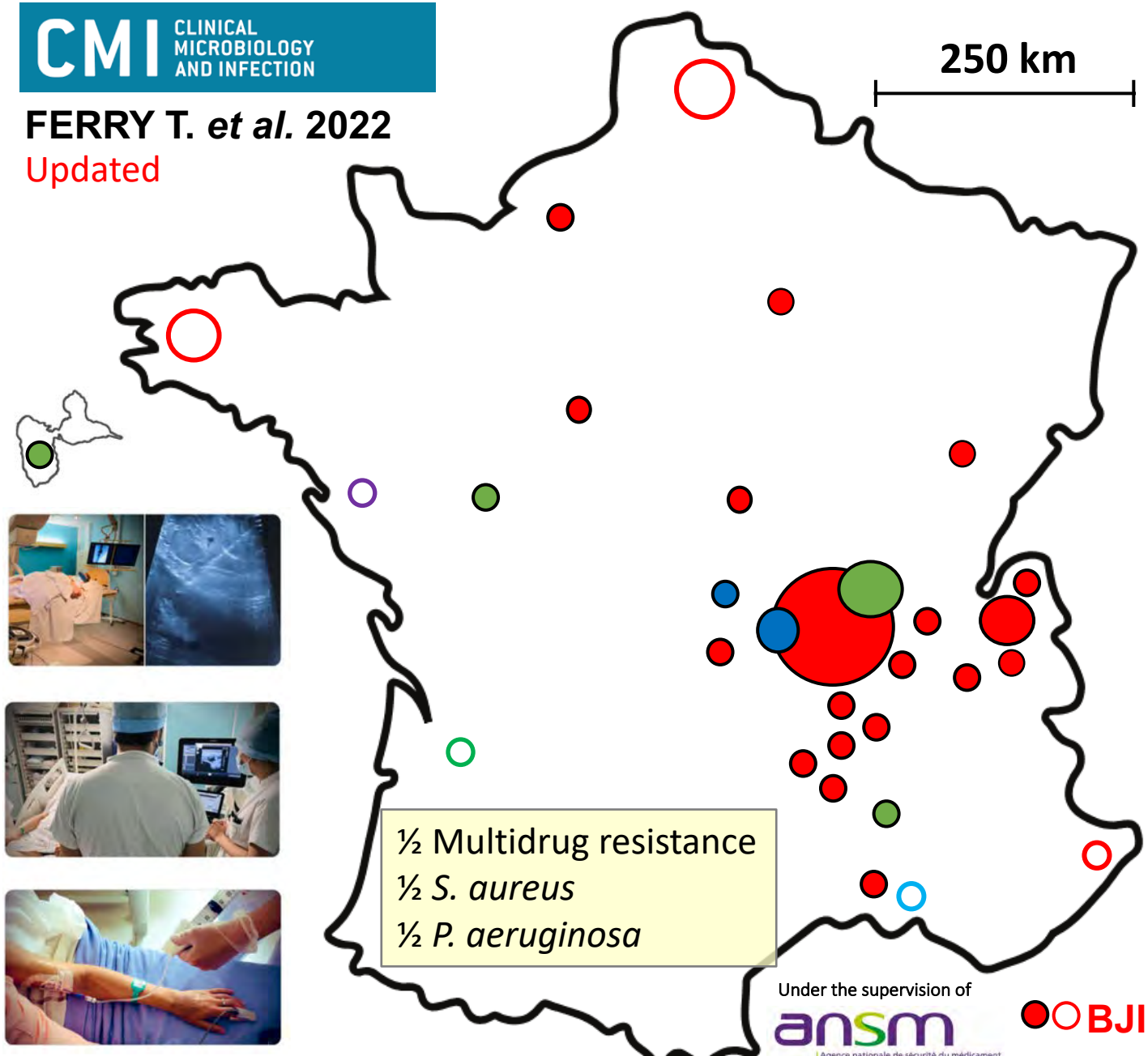
- 50 with phages from PHERECYDES PHARMA
- 3 with phages from MHKA HMRA

BJI · Endocarditis · Pneumonia · Burn

Implementation of a **Phage Therapy Center** in a CRIOAc

CMI CLINICAL MICROBIOLOGY AND INFECTION

FERRY T. *et al.* 2022
Updated



HCL HOSPICES CIVILS DE LYON — PHAGE*in*LYON — FONDATION HCL HOSPICES CIVILS DE LYON

Lyon 1 — CRIOAc LYON — ciri Centre International de Recherche en Infectiologie

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- 42 **BJI** (including **34 PJI**)
- 8 **endocarditis/vascular graft/ cardiac electronic device infection**
- 3 **lung infections** (VAP + bacteremia, pneumonia in lung graft bronchectasia, cystic fibrosis exacerbation)

+ 11 patients managed outside Lyon ○
including 1 in **and 1 in**

Implementation of a **Phage Therapy Center** in a CRIOAc

CMI CLINICAL MICROBIOLOGY AND INFECTION

FERRY T. *et al.* 2022
Updated

250 km

Visio RCP CRIOAc
Thérapie innovante

RCP Phagothérapie

+ 15 Patients
Treated with Lysins
CF-310 (PJI)

S. epidermidis

½ Multidrug resistance
½ *S. aureus*
½ *P. aeruginosa*

Under the supervision of ansm

HCL HOSPICES CIVILS DE LYON

PHAGE*in*LYON

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+ 11 patients managed outside Lyon ○
including 1 in and 1 in

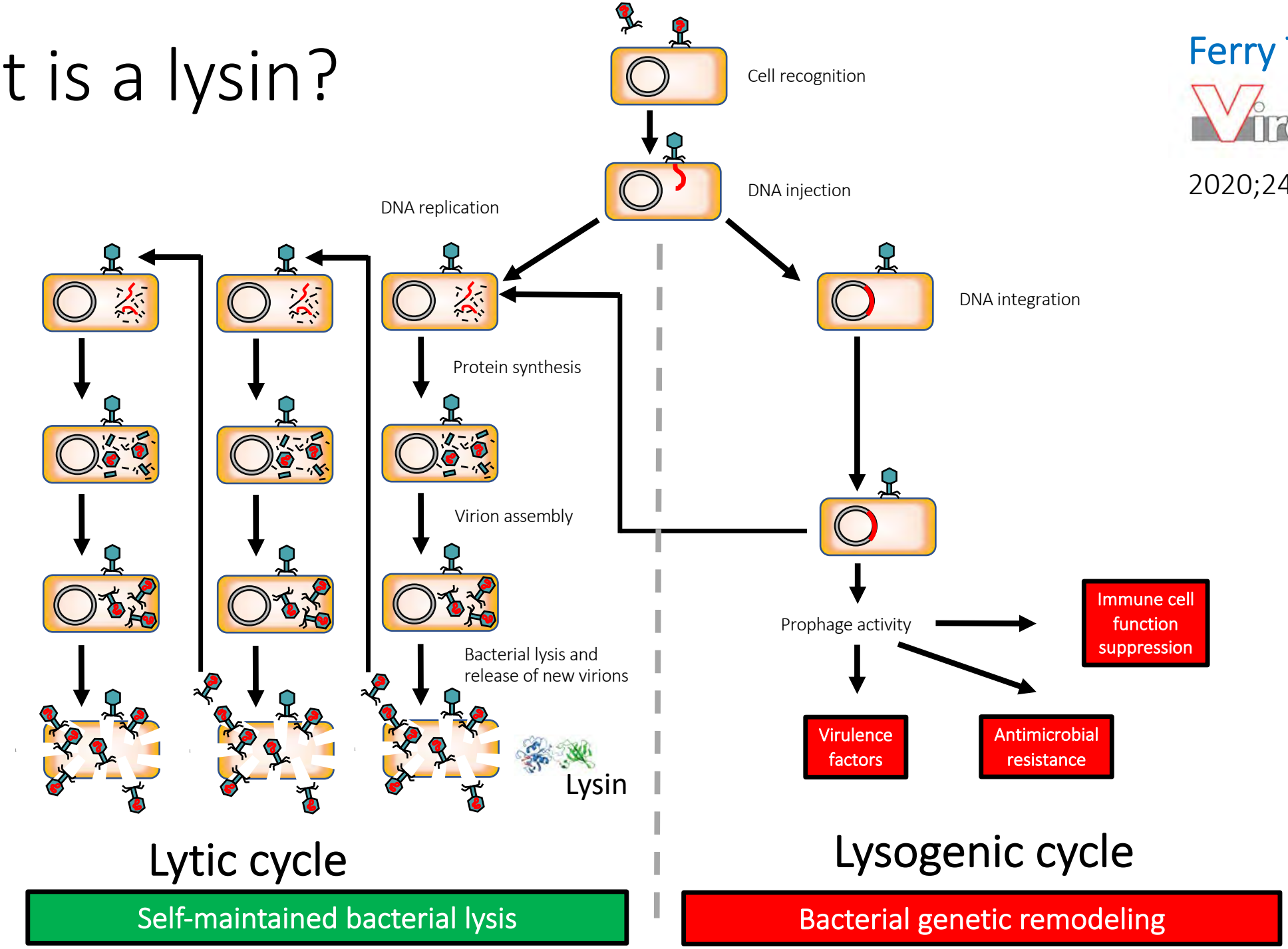
●○ **BJI** ●○ **Endocarditis** ●○ **Pneumonia** ●○ **Burn**

What is a lysin?

Ferry T. et al.

Virologie

2020;24(1):49-56



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

HCL
HOSPICES CIVILS DE LYON

30th ECCMID
Paris, France
18 –21 April 2020

frontiers in Medicine

ContraFect

CRIOAc LYON

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.

Essai thérapeutique CF-301-108

Essai thérateutique moocentrique @ CRIOAc LYON

Infection PTG à staphylocoques

Traitement par arthroscopie + Lysines de phages

3 mois de traitement antibiotiques

Recrutement régional et extrarégional

Suivi conjoint possible

CF-301-108

Randomized

Clinical Trial

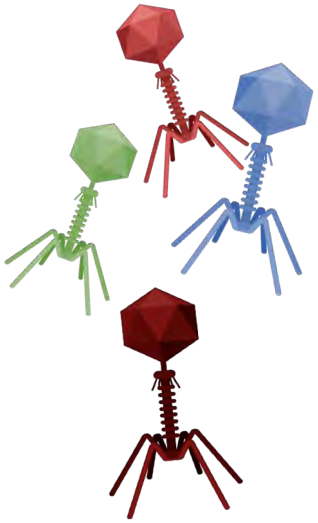
Press release April 2023

CONTRAFECT ANNOUNCES INITIATION OF A PHASE 1B/2 STUDY OF EXEBACASE IN PATIENTS WITH CHRONIC PROSTHETIC JOINT INFECTIONS OF THE KNEE

CRIOAc LYON

Développement de la phagothérapie à Lyon

PHAGE*in*LYON



PHAGE*in*LYON Clinic

Tristan Ferry

T. Ferry

Développement clinique
RCP CRIOAc Thérapies innovantes
RCP Phagothérapie
Validation des indications
Prise en charge des patients
Etudes de cohortes
Essais thérapeutiques

Infections ostéo-articulaires : Lyon devient le centre expert national pour la phagothérapie

Le centre de référence des infections ostéo-articulaires complexes, basé aux Hospices civils de Lyon, va centraliser toutes les demandes concernant ce traitement de dernier recours, utilisant des virus contre des bactéries résistantes.

Le Progrès – 23 févr. 2023 à 17:51 | mis à jour le 23 févr. 2023 à 18:08 – Temps de lecture : 2 min

RCP CRIOAc
Thérapie innovante

MINISTÈRE
DE LA SANTÉ
ET DE LA PRÉVENTION
Liberté
Égalité
Fraternité

Dédiée aux thérapies non traditionnelles (OMS)

Développement de la phagothérapie à Lyon

PHAGE*in*LYON

PHAGE*in*LYON Lab

Pargade Architectes

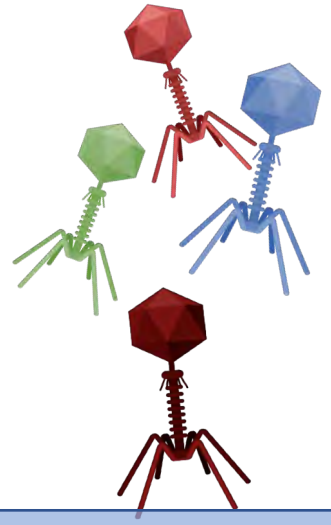
F. Laurent

PHAG-ONE

MINISTÈRE DE L'ENSEIGNEMENT SUPÉRIEUR, DE LA RECHERCHE ET DE L'INNOVATION

Liberté Égalité Fraternité

Recherche et développement
Production de phages publiques
Développement du phagogramme



Completer l'arsenal des phages à disposition

Essais thérapeutiques

PHAGE*in*LYON Clinic

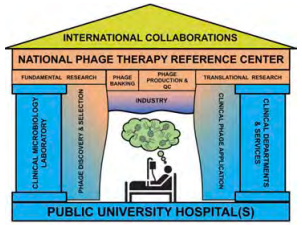
Tristan Ferry

T. Ferry

Développement clinique
RCP CRIOAc Thérapies innovantes
RCP Phagothérapie
Validation des indications
Prise en charge des patients
Etudes de cohortes
Essais thérapeutiques

Conclusion

- La phagothérapie est une **thérapie innovante et réémergente**
- **Recherche translationnelle**
- **Microbiologie, collaborations avec des industriels, études de cohorte**
- **En ADJUVANT à l'antibiothérapie (et potentiellement la chirurgie)**
- **Traitements compassionnels**
- Nécessité d'une **mission nationale « CRIOAc thérapie innovante »**
  - Pour valider les **indications pertinentes** de phages/lysines dans les IOA
  - Pour orienter les prises en charge vers les **essais thérapeutiques**
  - Ou enfin pour **orienter et accompagner** le recours à des phages en « compassionnel » (nécessité d'une mission nationale **« RCP Phagothérapie »** pour préciser les modalités)
- Poser les jalons d'un **centre national de phagothérapie**
- Conception et réalisation d'**essais thérapeutiques**



ESGNTA
ESCMID STUDY GROUP FOR NON-TRADITIONAL ANTIBACTERIAL THERAPY
European Society of Clinical Microbiology and Infectious Diseases

THE MYTHOLOGY
OF PHAGE THERAPY

T. FERRY

T. FERRY

Lyon BJI Study group

Coordinator: Tristan Ferry

Infectious Diseases Specialists – Tristan Ferry, Florent Valour, Thomas Perpoint, Florence Ader, Sandrine Roux, Agathe Becker, Claire Triffault-Fillit, Anne Conrad, Cécile Pouderoux, Pierre Chauvelot, Paul Chabert, Johanna Lippman, Evelyne Braun

Surgeons – Sébastien Lustig, Elvire Servien, Cécile Batailler, Stanislas Gunst, Axel Schmidt, Elliot Sappey-Marinier, Quentin Ode, Michel-Henry Fessy, Anthony Viste, Jean-Luc Besse, Philippe Chaudier, Lucie Louboutin, Adrien Van Haecke, Marcelle Mercier, Vincent Belgaid, Aram Gazarian, Arnaud Walch, Antoine Bertani, Frédéric Rongieras, Sébastien Martres, Franck Trouillet, Cédric Barrey, Ali Mojallal, Sophie Brosset, Camille Hanriat, Hélène Person, Samuel Prive, Philippe Céruse, Carine Fuchsmann, Arnaud Gleizal;

Anesthesiologists – Frédéric Aubrun, Mikhail Dziadzko, Caroline Macabéo, Dana Patrascu;

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

Imaging – Fabien Craighero, Loic Boussel, Jean-Baptiste Pialat, Isabelle Morelec;

PK/PD specialists – Michel Tod, Marie-Claude Gagnieu, Sylvain Goutelle;

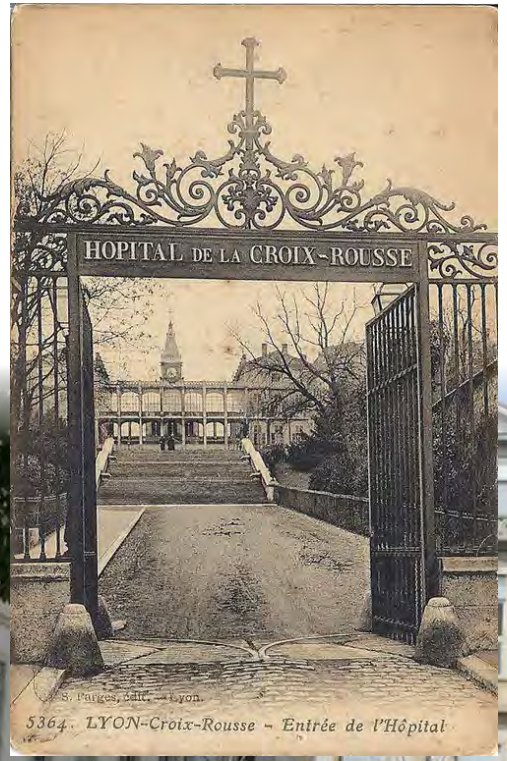
Clinical research assistant and database manager– Eugénie Mabrut

PHAGE*in*LYON *Clinic*

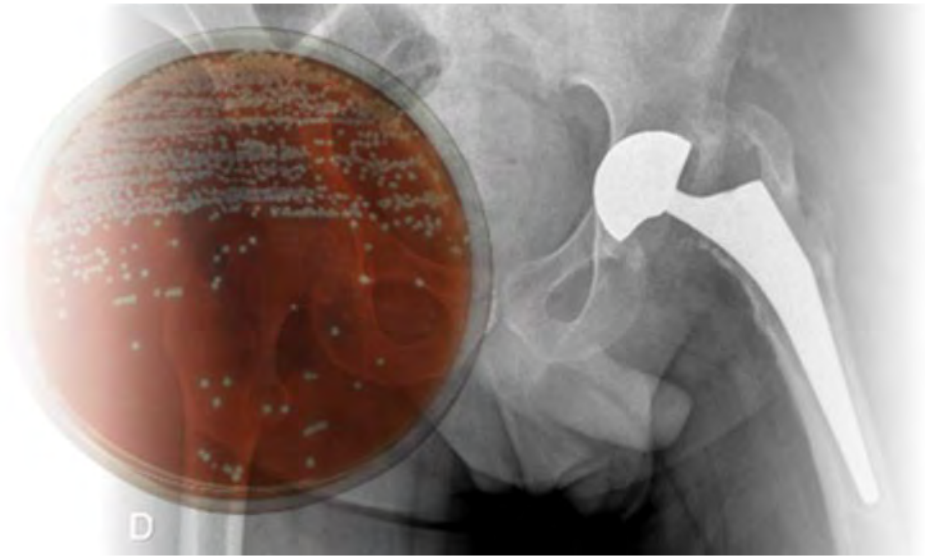
Coordinator: Tristan Ferry

Tristan Ferry, Myrtille Le Bouar, Gilles Leboucher, Thomas Briot, Camille Kolenda, Tiphaine Roussel-Gaillard, Karine Dallosto

Croix-Rousse Hospital



http://www.crioac-lyon.fr



- Published cases
- Open acces studies in pdf
- All thesis in pdf
- All recommendations
- **Newsletter**

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