Preparations & Formulations for phage therapy

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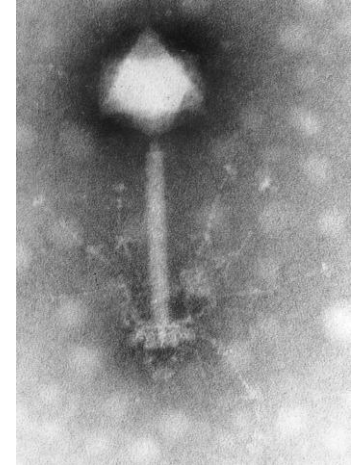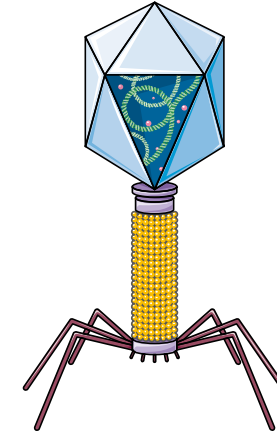
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6 / 7 / 8 OCTOBRE 2021
HYÈRES - FRANCE

Programme
PHAGEinLYON

HCL HOSPICES CIVILS DE LYON
FONDATION HCL HOSPICES CIVILS DE LYON

PHAG-ONE

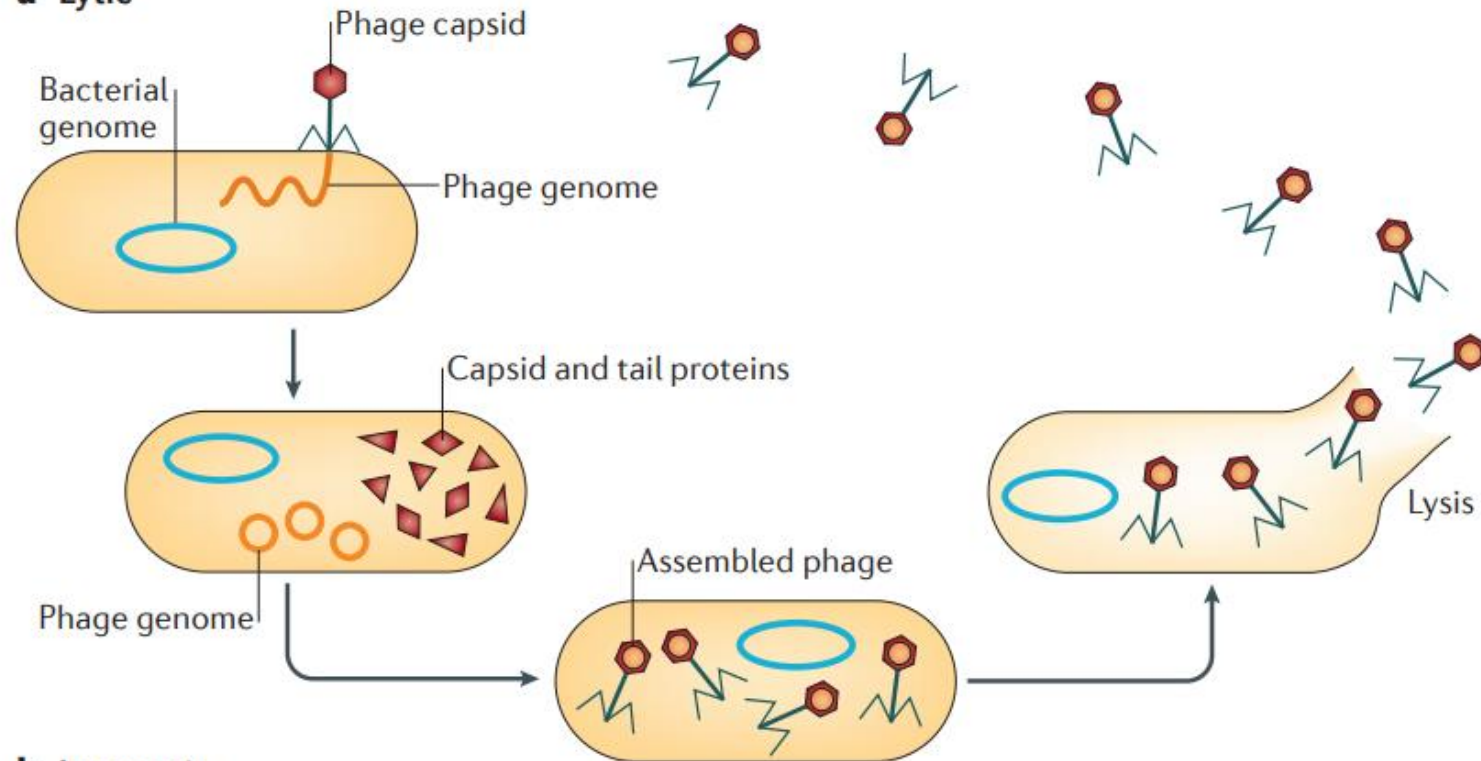anr agence nationale de la recherche

What are Bacteriophages?

- Discovered in 1915 (William Twort)

- Non-living organisms (viruses)

- Abundant and ubiquitous in environment

- Able to infect and kill bacteria (Felix d'Herelle 1917)
  - Specific to bacteria
  - Unable to infect eukaryote cells

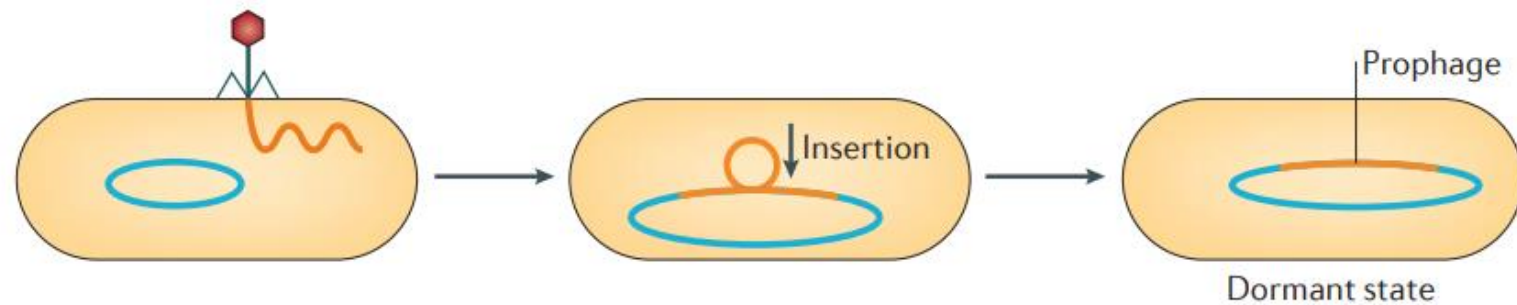- A protein capsid surrounding a nucleic acid (RNA or DNA) and a tail

Mann NH, *PLoS Biology Vol.*, 2005

Cycles of replication

a Lytic

Phage capsid

Bacterial genome

Phage genome

Capsid and tail proteins

Phage genome

Assembled phage

Lysis

b Lysogenic

Insertion

Prophage

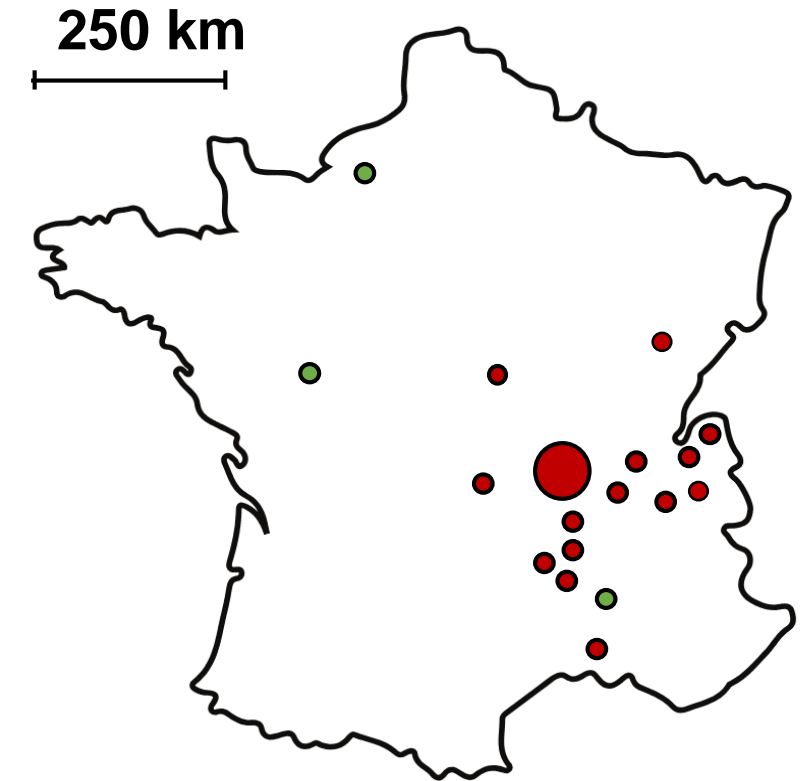Dormant state

Feiner et al. *Nat Rev Microbiol.,* 2015

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Medical context

- **Multiple antibiotic-resistant bacteria infections**

- **Bone and joint infections**
  - Prosthesis replacement not possible or low probability of success
  - 24 patients (20 for prosthesis infections)

- **Endocarditis**
  - 3 patients

- **Pathogens*:***
  - *Staphylococcus aureus*
  - *Pseudomonas aeruginosa*
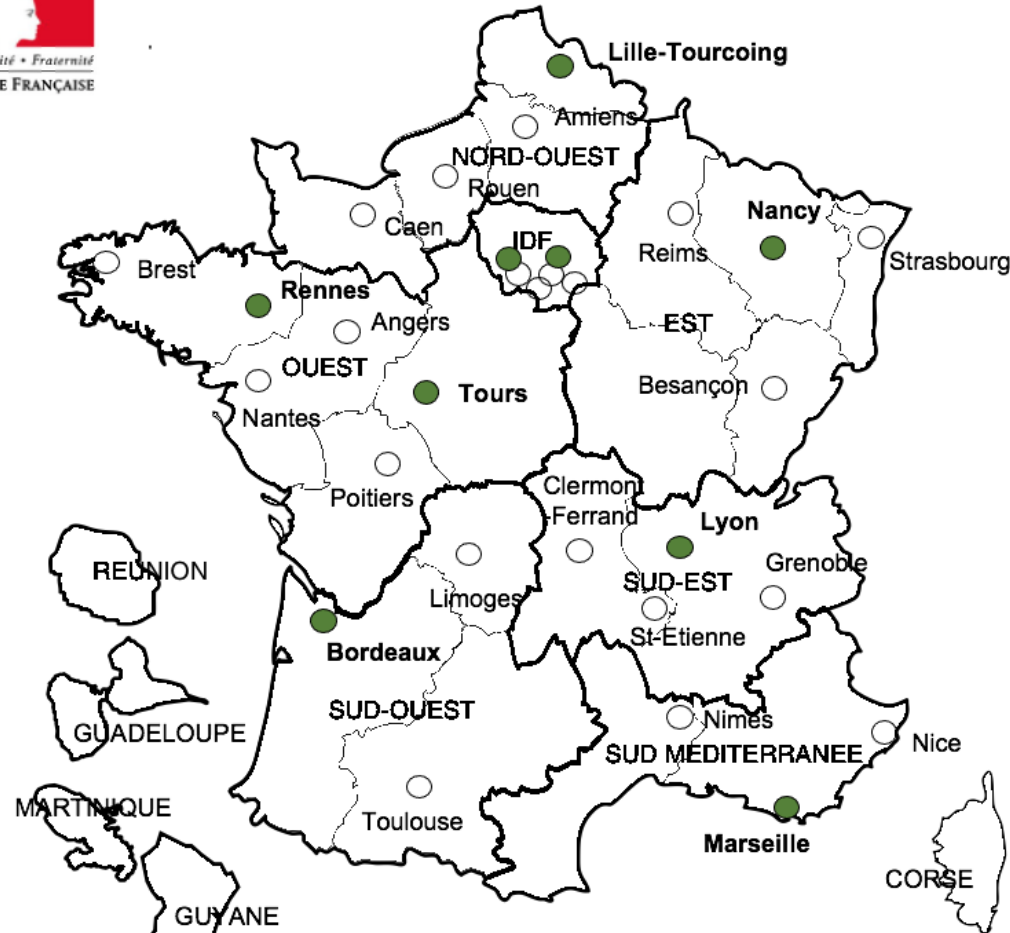 - *Staphylococcus epidermidis*
  - *Staphylococcus caprae*

250 km

Ferry T. et al. *Clin Micro Infect.,* 2021 *(In press)*

Medical context

REFERENCE CENTERS FOR THE MANAGEMENT OF BONE AND JOINT INFECTION

Ferry T. et al. *Orthop Traumatol Surg Res.,* 2019

Regulatory status

- **Bacteriophages are not:**
  - Medicines (according to the French definition)
  - Approved by FDA or EMA
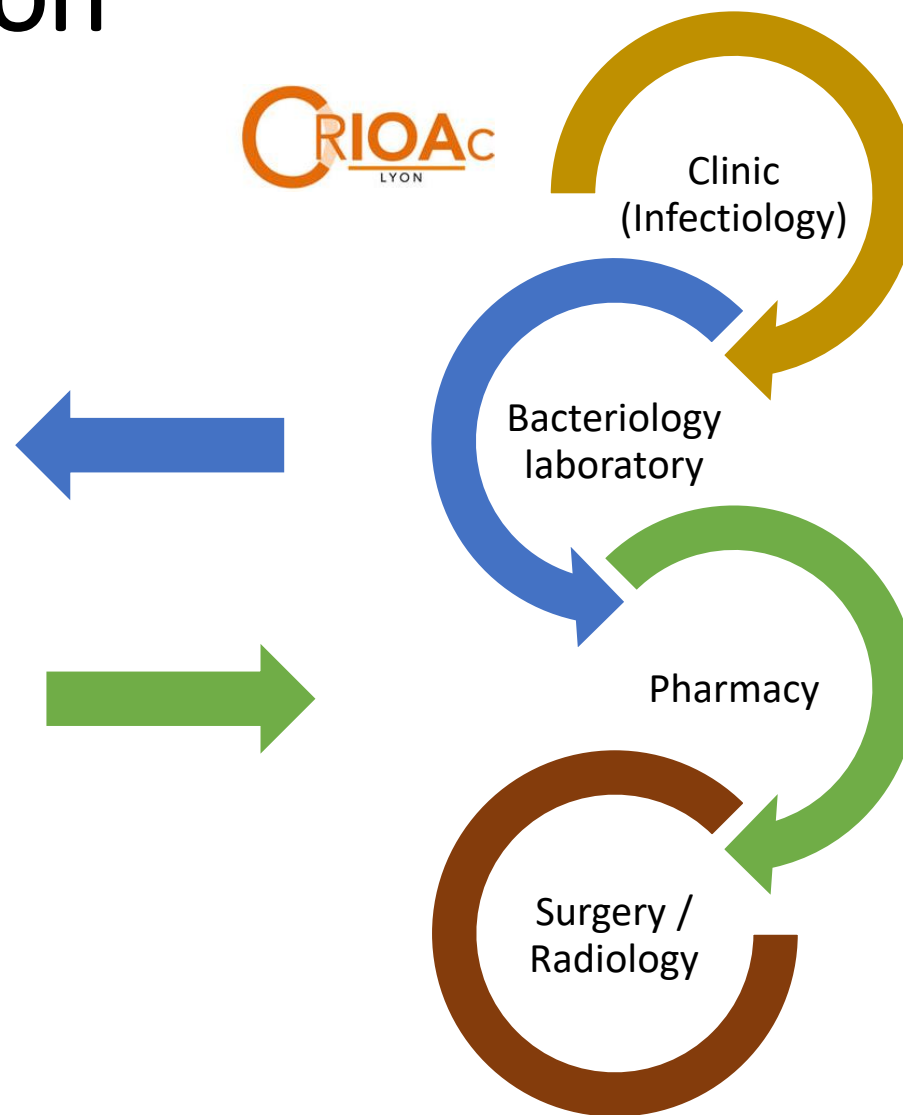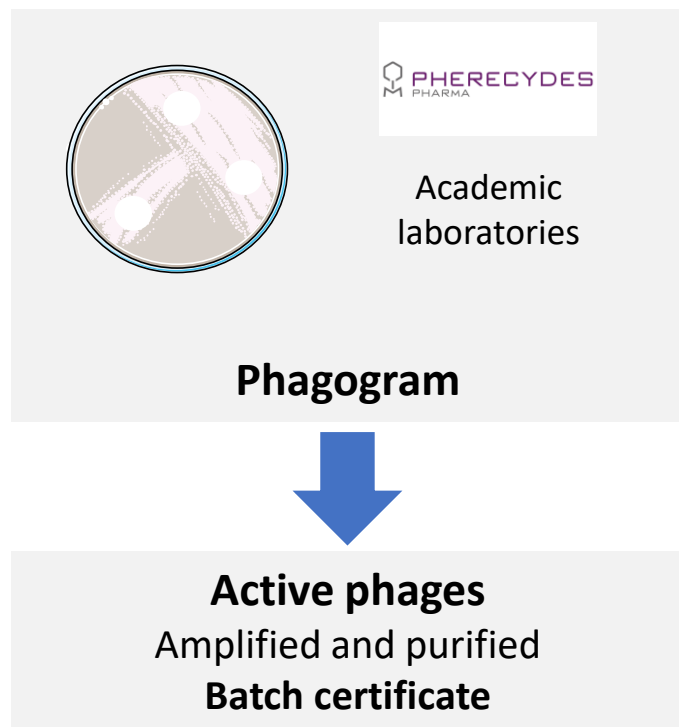 - Under the status of Temporary Use Authorization of the ANSM

- **In Belgium**, Active Pharmaceutical Ingredients (described in the Belgian Pharmacopeia)

- **In US**, emergency investigational new drug (eIND) pathway of the FDA

- **In France**, Pherecydes Pharma provides bacteriophages for compassionate use

Organization in Lyon

Formulations developed (extemporaneous magistral preparations)

- **Suspensions**
  - Local delivery: when a cavity is available (bone or prosthetic joint infection)
  - Intravenous: for endocarditis and prosthetic joint infection

- **Hydrogel**
  - To apply directly on the bone
    - Release of phages from hydrogel*
    - Phages remain active after 6 hours (at least)*
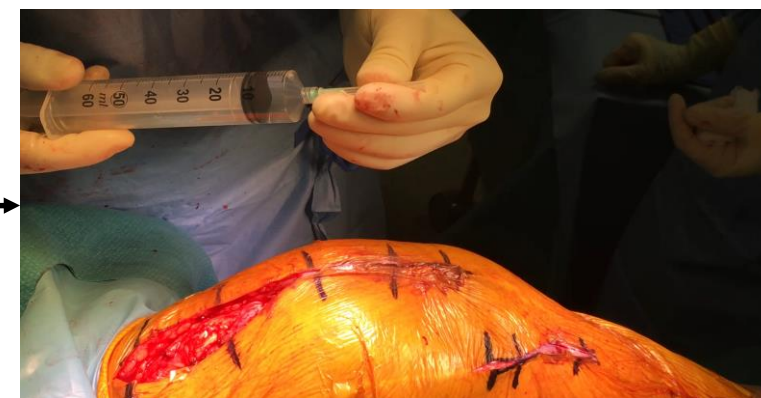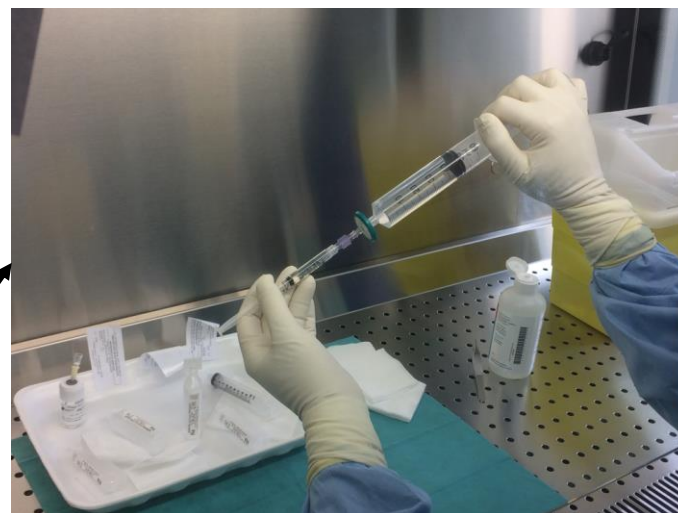
*Ferry T. et al, Front Med, 2020.

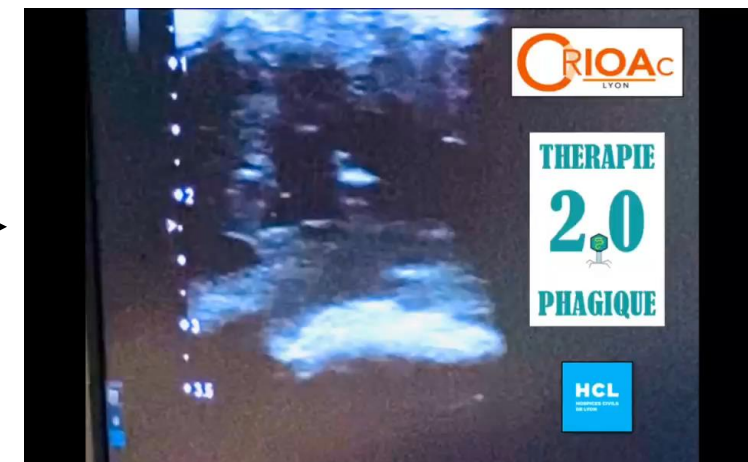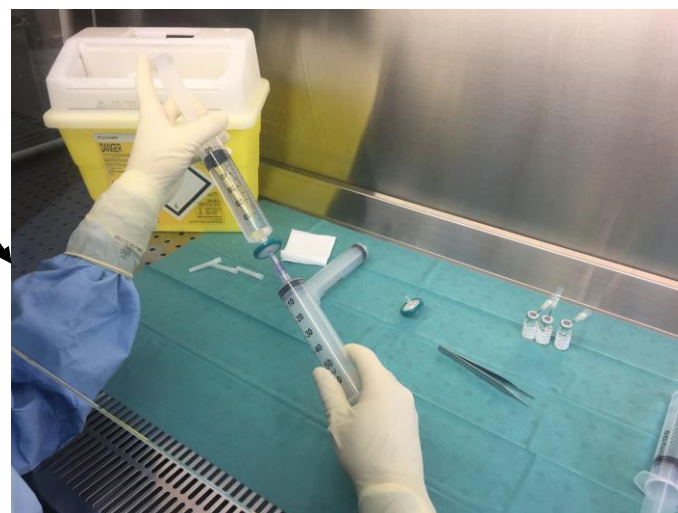# Formulations developed

- **Aseptic room:**
  - Class A into B (according to French "*Bonnes Pratiques de Préparation*")
- **Final filtration**
  - 0.22μm
- **Medical devices**
- **Solvent/Diluent**
- **Waste treatment**
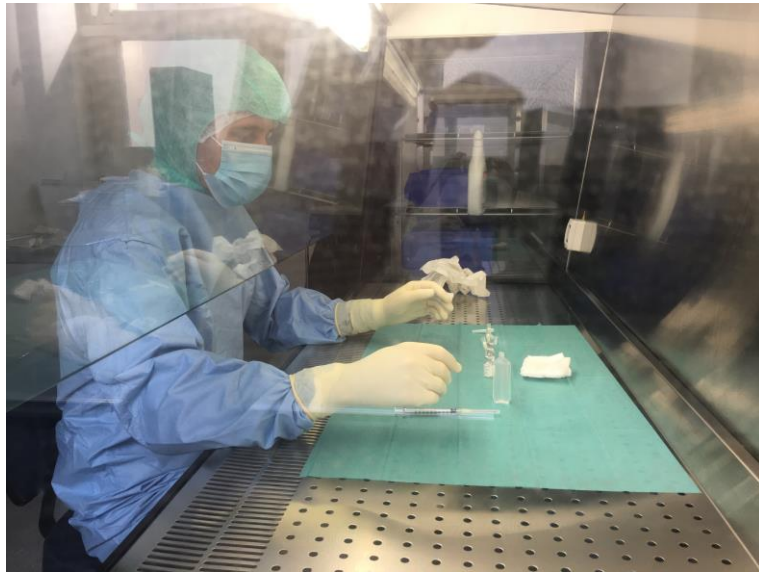- **Decontamination procedures**

Formulations developed: suspensions

Ferry T et al. *Open Forum Infect Dis,* 2018

Formulations developed: hydrogel

Dilution of phages under aseptic conditions

Pharmacist in charge of hydrogel reconstitution

Operating room

Hydrogel applied on the tibia

Quality controls performed currently

- According to European Pharmacopoeia (Injectable preparations)
  - Sterility
  - Endotoxin assay
  - Titer (when possible)

- Parametric controls
  - Atmospheric controls
  - Validation of the process:
    - Qualified staff
    - Qualified medical devices (adsorption phenomena)

Before starting

- Risk analysis

- Validation by legal department of the hospital

- Collaboration with infectiology, microbiology, surgery departments

- Reference centers for bone and joint infections or others multi-resistant infections

- Discussion with health authorities (ANSM in France)

- Pharmacovigilance center able to manage and analyze information on suspected adverse reactions due to bacteriophages

- Information of the patient and patient's approval

Conclusion

- **Great experience**

- **Multidisciplinary team**
  - Infectiology
  - Microbiology
  - Pharmacy
    - Preparations
    - Controls (in collaboration with FRIPHARM team)
  - Surgery

- **Drug repurposing**
- **Status of bacteriophages may be better defined**
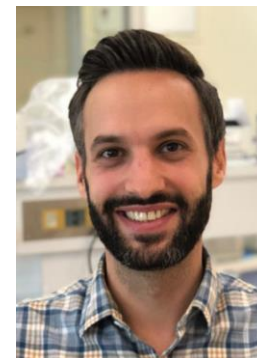
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