Conservative management of chronic infections: Experience with subcutaneous antimicrobial suppressive treatment and bacteriophages

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#### Two major issues, sometimes combined



AMR: Antimicrobial resistance







T. Ferry et al. Chapter in the book "Infection in Knee Replacement" on behalf of Springer and ISAKOS, 2021

#### Risk for chronic infection with a fistula



#### 57-year-old man with chronic osteomyelitis



#### Risk for chronic infection with a fistula



#### BMJ Case Rep 2018

#### Chronic and severe prosthetic joint infection complicated by amyloid A amyloidosis with renal and bladder impairment

Nicolas Benech,<sup>1</sup> Sebastien Lustig,<sup>1,2,3,4</sup> Christian Chidiac,<sup>1,2,4,5</sup> Tristan Ferry,<sup>1,2,4,5</sup> on behalf of Lyon BJI Study group

66-year-old woman Bone resection for tumor

Prosthetic-knee infection 2-stage exchange Failure in 2002 Lost to follow-up

15 years later Fistula End-stage kidney injury



### Risk for chronic infection with a fistula







Non-Operative Management of Chronic Infections Curative surgery not feasible

- Find the pathogen(s) (surgery or joint puncture or US/CT guided bone biopsies)
- Discuss a <u>conservative surgery:</u>
  - Several gold standard samples to find pathogen(s)
  - Reduction of the inocula (planktonic)
  - Fistulectomy (pathology)
- Start <u>empirical</u> and then <u>primary antimicrobial therapy (6w to 12w)</u>
- Then switch to suppressive antimicrobial therapy (SAT)







Consensus document

2017

Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

Some patients may be considered **unsuitable for implant removal**, either because they present with **too many baseline conditions**, or because a **poor functional outcome is foreseen**. In these patients, prolonged or <u>indefinite</u> antimicrobial therapy aiming **to control the infection may be considered**. This strategy is known as **SAT (suppressive antimicrobial therapy)**.

Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America<sup>a</sup>





Douglas R. Osmon,<sup>1</sup> Elie F. Berbari,<sup>1</sup> Anthony R. Berendt,<sup>2</sup> Daniel Lew,<sup>3</sup> Werner Zimmerli,<sup>4</sup> James M. Steckelberg,<sup>1</sup> Nalini Rao,<sup>5,6</sup> Arlen Hanssen,<sup>7</sup> and Walter R. Wilson<sup>1</sup>



Microorganism	Preferred Treatment	Alternative Treatment
Staphylococci, oxacillin-susceptible	Cephalexin 500 mg PO tid or qid or Cefadroxil 500 mg PO bid	Dicloxacillin 500 mg PO tid or mil Clindamycin 300
Staphylococci, exacillin-resistant	Cotrimoxazole 1 DS tab PO bid Minocycline or do	xazole, tetracj
β-hemolytic streptococci	damycin, cotrinic	Cephalexin 500 mg PO tid or qid
eta-lactam, clin	or Amoxicillin 500 mg PO tid	
seudomonas aeruginosa	Ciprofloxacin 250-500 mg PO bid	
Enterobacteriaceae	Cotrimoxazole 1 DS tab PO bid	β-lactam oral therapy based on in vitro susceptibilities
Propionibacterium spp	Penicillin V 500 mg PO bid to qid or Amoxicillin 500 mg PO tid	Cephalexin 500 mg PO tid or gid Minocycline or doxycycline 100 mg PO

#### Clinical Infectious Diseases 2013;56(1):e1–25



Figure 1. Clinical outcome of 38 patients with prosthetic joint infections treated with prolonged suppressive antibiotic therapy. Kaplan-Meier curve showing survival without event (95% confidence interval in grey). Events are defined as failure and unrelated death.

#### Prendki et al. International Journal of Infectious Diseases (2014)

#### **Potential risk for failure of SAT:**

- Fistula
- Comorbidities
- No surgery (conservative surgery)
- No primary antimicrobial therapy
- Duration of primary antimicrobial therapy
- Use of anti-bioflm agent during primary therapy
- Type of drug used for SAT
- Dose used for SAT

Wouthuysen-Bakker et al. J. Bone Joint Infect. 2017 Prendki et al. International Journal of Infectious Diseases. 2014 Ariza J et al. Enferm Infecc Microbiol Clin. 2017 Escudero-Sanchez R et al. Clin Microbiol Infect. 2019 Segreti J et al. Clin Infect Dis. 1998 Sandiford NA et al. Eur J Orthop Surg Traumatol. 2020 Pradier M et al. Infection. 2018



Figure 1. Clinical outcome of 38 patients with prosthetic joint infections treated with prolonged suppressive antibiotic therapy. Kaplan-Meier curve showing survival without event (95% confidence interval in grey). Events are defined as failure and unrelated death.

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## Personalized medicine for BJI

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

Antibiotic-loaded bone substitutes

# ADJUVANT INNOVATIVE ANTI-INFECTIVE AGENTS



Bacteriophages

Bacteriophage-derived lysins

New antibiotics targeting the biofilm

OPTIMAL<br/>SEPTIC<br/>SURGERYTARGETED AND<br/>OPTIMAL<br/>OPTIMAL<br/>ANTIMICROBIAL<br/>THERAPY

New antibiotics usable for SAT

Subcutaneous personalized SAT

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MEDICAL

INNOVATIVE

**STRATEGIES** 

**TO KEEP** 

THE FUNCTION

Subcutaneous personalized SAT

# What is a bacteriophage?

Class

Aph

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- devour"Viruses that infect ONLY bacteria
  - **Hypothesis:**

• Suffix –phage, phagos φαγεῖν (phagein), "to eat", "to

- Large Use of bacteriophages increase lages
  on the success rate of SAT ater,
  - soil, animal and human stools, etc.
- Phages have **antibiofilm** activity (Lyon *in vitro* models)
- Use <u>lytic</u> and <u>pharmaceutical-quality</u> phages (not easily available at the present time)









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



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





#### **Open Forum Infectious Diseases**

BRIEF REDO



frontiers in Medicine The Potential Innovative Use of Bacteriophages Within the DAC® Hydrogel to Treat Patients With Knee

ection Requiring

and Soft Tissue

2020

biotics and

ge Therapy

ction

Study Group

te Petitjean<sup>6</sup>, Joseph Chateau<sup>7</sup>, rosset7, Gilles Leboucher9,

one and joint

including local





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Salvage De an Elderly 1 Staphyloco Infection?

**Case Report: Arthroscopic Frontiers** in Medicine "Debridement Antibiotics and Implant Retention" With Local Implant Re Injection of Personalized Phage Local Injec Therapy to Salvage a Relapsing of Bacterior Pseudomonas Aeruginosa Prosthetic **Knee Infection** 2021

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

Ferry T.

ntiers

Medicine

application of a selected cocktail of bacteriophages Tristan Ferry 🖾, Fabien Boucher, Cindy Fevre, Thomas Perpoint, Joseph Chateau, Charlotte Petitjean,

Jérôme Josse, Christian Chidiac, Guillaume L'hostis, Gilles Leboucher, ... Show more

Journal of Antimicrobial Chemotherapy, Volume 73, Issue 10, 1 October 2018, Pages 2901–2903,



### **Clinical case** (not published; 16<sup>th</sup> treated patient)

- 62-year-old woman
- Leiomyosarcoma
- Radiotherapy
- Fracture
- Osteosynthesis, soft tissue flap
- 2-stage exchange of a nail
- **Recurrent S. aureus infection**
- Proximal and distal **abscesses**



















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Proximal and distal abscesses





No surgery Personalized **phage cocktail One shot** phage injection





#### Highly purified phage cocktail 10<sup>9</sup> phages/mL



No surgery

Personalized phage cocktail

One shot phage injection

Primary then suppressive antimicrobial therapy (cephalexin)

**Favorable outcome at 12 months** 





No surgery

Personalized phage cocktail

One shot phage injection

Primary then suppressive antimicrobial therapy (cephalexin)

#### **Favorable outcome at 12 months**





No surgery

Personalized phage cocktail

One shot phage injection

Primary then suppressive antimicrobial therapy (cephalexin)

#### **Favorable outcome at 12 months**





"I acknowledge so much Pr. Ferry and the PHAGEinLYON team, thanks to them, I save precious time!"

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# TédiSAT study (Oral Session, Dr. PHAM)







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Tedizolid

Activity on multidrug-resistant Gram positive pathogens 1 pill per day **Open Forum Infectious Diseases** 

BRIEF REPORT 2021

Safety of Tedizolid as Suppressive Antimicrobial Therapy for Patients With Complex Implant-Associated Bone and Joint Infection due to Multidrug-Resistant Gram-Positive Pathogens: Results From the TediSAT Cohort Study

Tristan Ferry,<sup>1,2,3</sup> Anne Conrad,<sup>1,2,3</sup> Eric Senneville,<sup>4,5,6</sup> Sandrine Roux,<sup>1,2</sup> Céline Dupieux-Chabert,<sup>1,2,3</sup> Aurélien Dinh,<sup>7,8</sup> Sébastien Lustig,<sup>2,9</sup> Sylvain Goutelle,<sup>1,2,10,©</sup> Thomas Briot,<sup>1,2</sup> Truong-Thanh Pham,<sup>1,2,11,©</sup> Florent Valour<sup>1,2,3</sup>

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# #OSCAT





Outpatient SubCutaneous Antimicrobial Therapy (OSCAT) as a Measure to Improve the Quality and Efficiency of Healthcare Delivery for Patients with Serious Bacterial Infections



Tristan Ferry,<sup>1,2,3,4</sup> Thomas P. Lodise,<sup>5</sup> Jason Gallagher,<sup>6</sup> Emmanuel Forestier,<sup>7</sup> Sylvain Goutelle,<sup>8,9</sup> Vincent H. Tam,<sup>10</sup> John F. Mohr, III,<sup>11</sup> Claire Roubaud-Baudron<sup>12,13</sup>





J Antimicrob Chemother 2019; 74: 2060-2064 doi:10.1093/jac/dkz104 Advance Access publication 10 April 2019







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Cécile Pouderoux<sup>1-3</sup>\*, Agathe Becker<sup>1-3</sup>, Sylvain Goutelle () <sup>2-4</sup>, Sébastien Lustig<sup>2,3,5</sup>, Claire Triffoult-Fillit<sup>1-3</sup>, Fatiha Daoud<sup>1,3</sup>, Michel Henry Fessy<sup>2,3,6</sup>, Sabine Cohen<sup>2,7</sup>, Frédéric Laurent<sup>2,3,8,9</sup>, Christian Chidiac<sup>1-3</sup>, Florent Valour<sup>1-3,9</sup> and Tristan Ferry<sup>1,3,9</sup> on behalf of the Lyon Bone and Jaint Infection Study Group†

#### Ceftriaxone, ertapénème, ceftazidime, céfépime

frontiers in Medicine 2020









Pharmacokinetic/Pharmacodynamic Dosage Individualization of Suppressive Beta-Lactam Therapy Administered by Subcutaneous Route in Patients With Prosthetic Joint Infection

Sylvain Goutelle<sup>1,2,3,4\*</sup>, Anne Conrad<sup>4,5,6,7</sup>, Cécile Pouderoux<sup>4,5</sup>, Evelyne Braun<sup>4,5</sup>, Frédéric Laurent<sup>2,4,7,8</sup>, Marie-Claude Gagnieu<sup>9</sup>, Sabine Cohen<sup>9</sup>, Jérôme Guitton<sup>2,9</sup>, Florent Valour<sup>4,5,6,7</sup> Tristan Ferry<sup>4,5,6,7</sup> on behalf of the Lyon BJI Study group





PharmD, PhD

# **Clinical case (not published)**

- 83-year-old man
- Comorbidity

#### **Prosthetic shoulder infection**

- Productive fistula
- No pain
- No loosening of the stem
- Serratia Marcesens
- No oral option
- **Ertapenem susceptible**



Cambrai 633 km Lyon











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Injections only 3 times per week



Prediction of ertapenem exposition, depending on host characteristics and MIC







# Outcome **3 injections per week**













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# Conclusion

- Patients with chronic BJI with a fistula
  - Need to be treated to avoid complications
- Infectious Disease physicians can:
  - Help to keep the function!
  - Develop and propose <u>personalized innovative anti-infective</u> <u>strategies</u> for selected <u>relevant indications</u>
- Phages have a real potential in prosthetic-joint infection
  - Need for <u>industrial and academic developement</u> of therapeutic phages (discovery, banking, susceptibility testing) in connection with health care authorities
- Personalized suppressive subcutaneous SAT
  - Need strong involvement of pharmacologists
  - Can help if no oral options are available
- Need to **perform clinical trials** to evaluate the ability of these innovations to improve the outcome



French Academy of Surgery















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# 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, 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





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# V<sup>ème</sup> congrès national des CRIOAc





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