INFEZIONI PROTESICHE MDR E INFEZIONI DELL'OSSO

Dr ssa Letizia Attala

Malattie Infettive

Ospedale Santa Maria Annunziata, Firenze

Epidemiologia

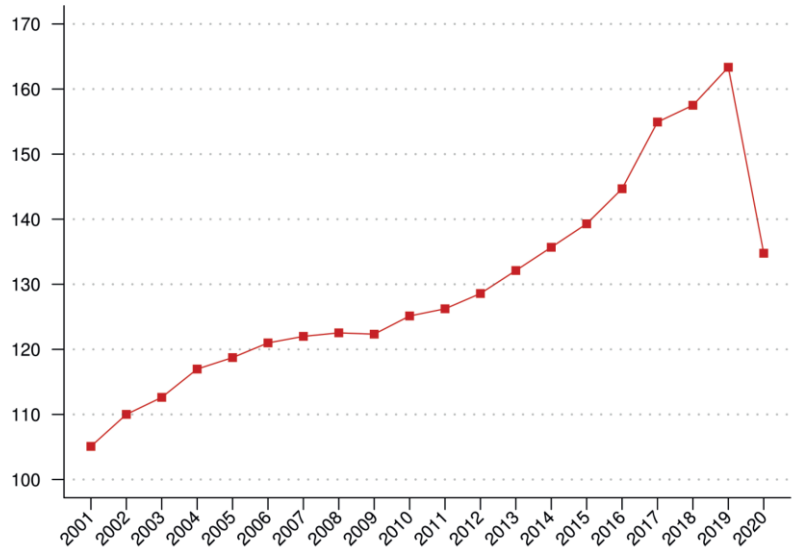
Incidenza delle infezioni periprotesiche:

- negli interventi primarie è del 2-3%
- negli interventi di revisione 10-20%

Secondo i dati del Registro italiano (Riap) relativi al 2020, l'infezione rappresenta:

- la quarta causa di fallimento di una protesi articolare nell'anca (11,3%)
- la terza causa nel ginocchio (16.7%) e nella spalla (13.8%)

Figura 6. Anca. Sostituzione totale e parziale in elezione (interventi principali e secondari). Indice d incidenza/ospedalizzazione nazionale. Anni 2001-2020



Procedura	2001	2003	2005	2007	2009	2011	2013	2015	2017	2019	2020
Anca	**74.408**	**80.999**	**87.499**	**91.077**	**93.241**	**96.125**	**100.844**	**105.803**	**112.375**	**117.910**	**98.507**
Sostituzione totale dell'anca	46.850	52.541	57.112	60.425	61.601	62.664	66.257	71.178	77.787	83.157	66.939
Sostituzione totale dell'anca in elezione	*40.060*	*44.505*	*47.908*	*50.684*	*51.769*	*53.157*	*56.598*	*60.656*	*66.917*	*71.625*	*55.869*
Sostituzione parziale dell'anca	21.394	21.753	23.227	23.119	23.393	25.091	25.979	26.222	26.101	25.876	24.292
Rivestimento totale dell'anca	0	0	0	0	293	162	99	107	65	229	256
Revisione di sostituzione dell'anca	6.164	6.705	7.160	7.533	7.954	8.208	8.509	8.296	8.422	8.648	7.020
Ginocchio	**28.693**	**38.655**	**47.643**	**57.054**	**61.079**	**63.749**	**67.634**	**73.191**	**81.271**	**89.210**	**67.826**

Original article

Progression and projection for hip surgery in France, 2008-2070: Epidemiologic study with trend and projection analysis

Roger Erivan[a,*], Guillaume Villatte[a], Julien Dartus[b,c], Nicolas Reina[d], Stéphane Descamps[a], Stéphane Boisgard[a]

A B S T R A C T

Introduction: Hip replacement was declared "operation of the century" in tribute to the functional improvement it provides. Frequency is increasing, but it is difficult to estimate the actual number of procedures performed and the expected progression, because of changes in indications and lengthening life-expectancy, and also, in France, because there is no registry. As data are lacking in France, we conducted an investigation 1) to update the number of hip surgeries in France, and 2) to forecast progression over the coming decades, considering extreme scenarios.

Hypothesis: The number of hip procedures can be expected to increase considerably over the coming 50 years.

Material and method: A study was conducted to analyze national coding data for the number of hip surgeries performed in France. Two scenarios were defined: one taking account of population progression and age structure, the other also extrapolating trends observed over recent years. Current hip surgery activity in France was measured, and progression estimated according to population changes.

Results: In 2018 in France, 183,139 procedures were coded as principally concerning the hip. There was a clear predominance of reconstruction procedures, with 148,965 primary hip replacements, 124,251 of which were total. There were 19,304 hip replacement revision procedures. There were strong regional differences in revision according to the type of center performing surgery ($p < 0.0001$). Between 2018 and 2050, primary hip replacement could be expected to increase by 41.9% or 114.3% and hip surgery overall by 42.0% or 98.3%, depending on the scenario.

Discussion: The present results are subject to future technological breakthroughs and medical discoveries, but forecast a major increase in hip surgery requirements. These results extend the present state of medical knowledge.

- Diagnosi
- Tipologia trattamento chirurgico
- Biofilm
- Penetrazione ossea
- Patogeni MDR
- Timing durata della terapia
- Terapia soppressiva
- Altre terapie…

DIAGNOSI

The EBJIS definition of periprosthetic joint infection

A PRACTICAL GUIDE FOR CLINICIANS

Mancanza di un test di riferimento unico (*benchmark*) e assenza di una definizione univoca e universalmente accettata di infezione peri-protesica

La diagnosi di IPP sia attualmente basata su un approccio multimodale, in cui il "peso" dei singoli dati diagnostici nel determinare la diagnosi definitiva e estremamente variabile nei diversi studi e nelle diverse definizioni.

	Infection Unlikely (all findings negative)	**Infection Likely** (two positive findings)[a]	**Infection Confirmed** (any positive finding)
Clinical and blood workup			
Clinical features	Clear alternative reason for implant dysfunction (e.g. fracture, implant breakage, malposition, tumour)	1) Radiological signs of loosening within the first five years after implantation 2) Previous wound healing problems 3) History of recent fever or bacteraemia 4) Purulence around the prosthesis[b]	Sinus tract with evidence of communication to the joint or visualization of the prosthesis
C-reactive protein		> 10 mg/l (1 mg/dl)[c]	
Synovial fluid cytological analysis[d]			
Leukocyte count[c] (cells/µl)	≤ 1,500	> 1,500	>3,000
PMN (%)[c]	≤ 65%	> 65%	> 80%
Synovial fluid biomarkers			
Alpha-defensin[e]			Positive immunoassay or lateral-flow assay[e]
Microbiology[f]			
Aspiration fluid		Positive culture	
Intraoperative (fluid and tissue)	All cultures negative	Single positive culture[g]	≥ two positive samples with the same microorganism
Sonication[h] (CFU/ml)	No growth	> 1 CFU/ml of any organism[g]	> 50 CFU/ml of any organism
Histology[c,i]			
High-power field (400x magnification)	Negative	Presence of ≥ five neutrophils in a single HPF	Presence of ≥ five neutrophils in ≥ five HPF
			Presence of visible microorganisms
Others			
Nuclear imaging	Negative three-phase isotope bone scan[c]	Positive WBC scintigraphy[j]	

***Bone Joint J* 2021;103-B(1):18–25.**

Isolamento microbiologico

Colturale del liquido sinoviale

- in flaconi da emocolture per aerobi e anaerobi
- in incubazione per almeno 10 giorni

Prelevare un numero adeguato di campioni intra-operatori

- almeno 3, meglio 6
- Oltre i 6 non aumenta la sensibilità dgn ma solo il rischio di falsi positivi

Eseguire il campionamento microbiologico in wash out da terapia antibiotica

- Per ridurre i falsi negativi

Utilizzo di metodiche di microbiologia molecolare:

- pannello sindromico
- metagenomica

"Il BioFire® Joint Infection (JI) Panel è un test diagnostico *in vitro* basato sull'identificazione di acidi nucleici con tecnologia di amplificazione ***nested multiplex PCR*** da utilizzare con i sistemi BioFire® FilmArray® 2.0 e BioFire® FilmArray® Torch per la rilevazione qualitativa simultanea e l'identificazione di acidi nucleici di batteri, lieviti e determinati geni di resistenza antimicrobica da **liquido sinoviale** ottenuto da individui con **sospetta infezione articolare."**

BFI

PANNELLO BIOFIRE® JOINT INFECTION (JI)

1 TEST. 39 TARGET. ~ 1 ora

BATTERI GRAM-POSITIVI

Anaerococcus prevotii/vaginalis
Clostridium perfringens
Cutibacterium avidum/granulosum
Enterococcus faecalis
Enterococcus faecium
Finegoldia magna
Parvimonas micra
Peptoniphilus
Peptostreptococcus anaerobius
Staphylococcus aureus
Staphylococcus lugdunensis
Streptococcus spp.
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

BATTERI GRAM-NEGATIVI

Bacteroides fragilis
Citrobacter
Enterobacter cloacae complex
Escherichia coli
Haemophilus influenzae
Kingella kingae
Klebsiella aerogenes
Klebsiella pneumoniae group
Morganella morganii
Neisseria gonorrhoeae
Proteus spp.
Pseudomonas aeruginosa
Salmonella spp.
Serratia marcescens

LIEVITI

Candida spp.
- *Candida albicans*

GENI DI RESISTENZA ANTIMICROBICA

Carbapenemasi
IMP
KPC
NDM
OXA-48-like
VIM

ESBL
CTX-M

Resistenza alla meticillina
*mec*A/C e MREJ

Resistenza alla vancomicina
*van*A/B

Table 1
Description of prosthetic joint infection by time from arthroplasty

	Early Prosthetic Joint Infection	Delayed Onset (3–12 mo After Arthroplasty)	Late Onset
Synovial fluid			
White blood cell count (cells/μL)	>10,000	>3000	>3000
PMN (%)	>90	>80	>80
Serum CRP (mg/L)	>100[21]	>10	>10
Serum ESR (mm/h)	Not useful	>30	>30
Clinical presentation	Acute onset Wound drainage, fever, erythema, joint pain	Subacute joint pain; possible sinus tract formation, which diminishes pain	Systemic symptoms more likely with concomitant bacteremia, pain
Microbiologic differential	Virulent organisms *S aureus* Aerobic gram negative Polymicrobial Anaerobic	Less virulent Coagulase-negative staphylococci *Enteroccus* *Cutibacterium*	*S aureus* β-Hemolytic streptococci Gram-negative bacilli
Etiology	Acquired during arthroplasty	Acquired during arthroplasty, early postoperatively	Hematogenous from other infectious focus
Histopathology	More than 5 PMNs per high-power field in 5 high-power fields		

Infect Dis Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.idc.2018.06.005

APPROCCIO CHIRURGICO

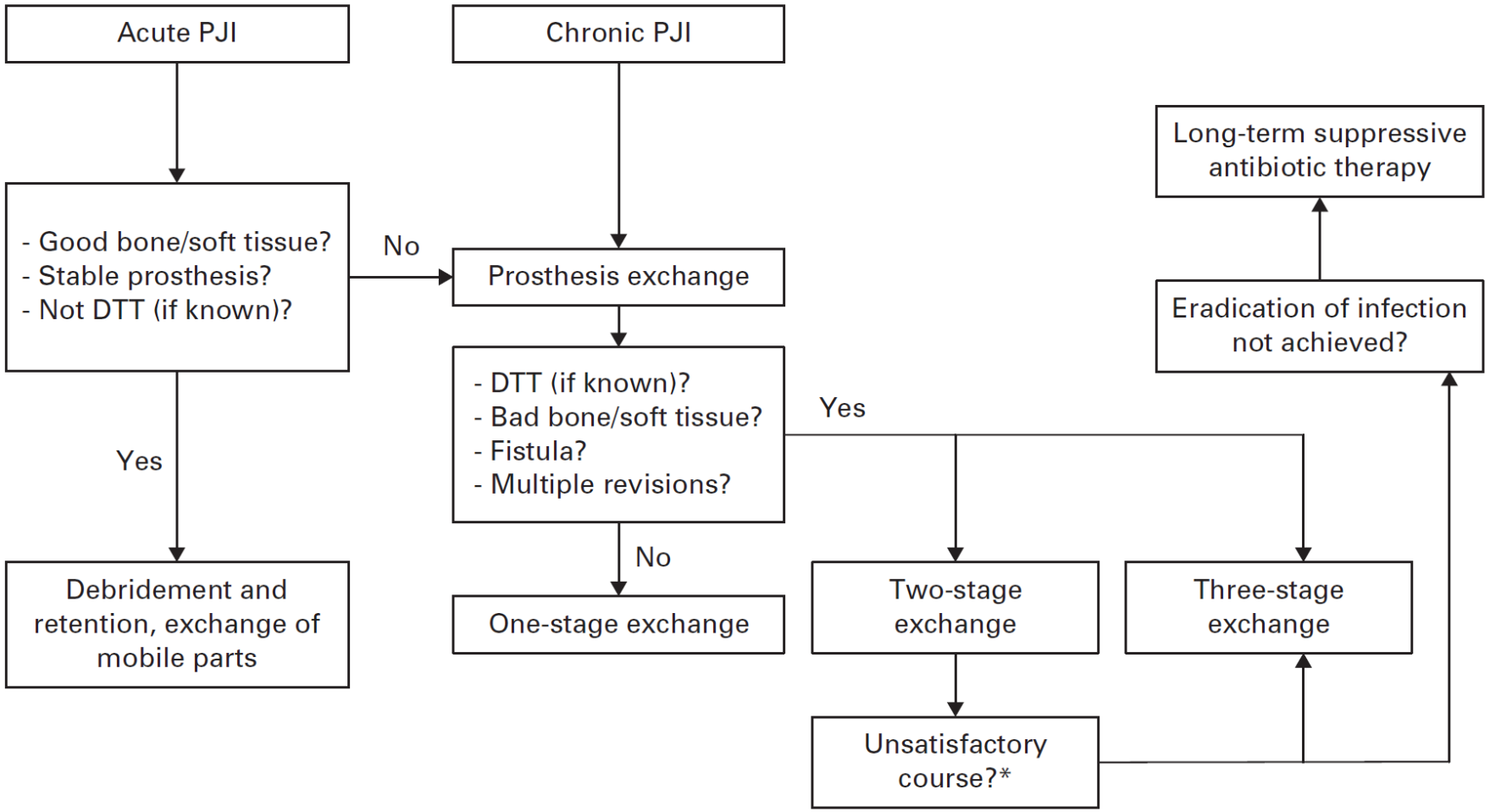


Fig. 1

Treatment algorithm for prosthetic joint infections (PJIs) dependent on acute/chronic and local situation using debridement, antibiotics, and implant retention (DAIR), one-stage-, two-stage-, and three-stage exchange options.[16] *Clinical signs of infection, elevated C-reactive protein (CRP), intraoperative pus, compromised tissue. DTT, difficult-to-treat infections caused by pathogens resistant to biofilm-active antimicrobials: rifampin-resistant staphylococci, ciprofloxacin-resistant Gram-negative bacteria, and fungi (*Candida*).

***Bone Joint J* 2019;101-B:132–139.**

BIOFILM

REVIEW ARTICLE OPEN

Evolving concepts in bone infection: redefining "biofilm", "acute vs. chronic osteomyelitis", "the immune proteome" and "local antibiotic therapy"

Elysia A. Masters[1,2], Ryan P. Trombetta[1,2], Karen L. de Mesy Bentley[1,3,4], Brendan F Boyce[1,3], Ann Lindley Gill[5], Steven R. Gill[5], Kohei Nishitani[1,6], Masahiro Ishikawa[1,6], Yugo Morita[1,6], Hiromu Ito[6], Sheila N. Bello-Irizarry[1], Mark Ninomiya[1], James D. Brodell Jr.[1], Charles C. Lee[1], Stephanie P. Hao[1], Irvin Oh[1,4], Chao Xie[1,4], Hani A. Awad[1,2,4], John L. Daiss[1,4], John R. Owen[7], Stephen L. Kates[7], Edward M. Schwarz[1,2,3,4,5] and Gowrishankar Muthukrishnan[1,4]

Osteomyelitis is a devastating disease caused by microbial infection of bone. While the frequency of infection following elective orthopedic surgery is low, rates of reinfection are disturbingly high. *Staphylococcus aureus* is responsible for the majority of chronic osteomyelitis cases and is often considered to be incurable due to bacterial persistence deep within bone. Unfortunately, there is no consensus on clinical classifications of osteomyelitis and the ensuing treatment algorithm. Given the high patient morbidity, mortality, and economic burden caused by osteomyelitis, it is important to elucidate mechanisms of bone infection to inform novel strategies for prevention and curative treatment. Recent discoveries in this field have identified three distinct reservoirs of bacterial biofilm including: *Staphylococcal* abscess communities in the local soft tissue and bone marrow, glycocalyx formation on implant hardware and necrotic tissue, and colonization of the osteocyte-lacuno canalicular network (OLCN) of cortical bone. In contrast, *S. aureus* intracellular persistence in bone cells has not been substantiated in vivo, which challenges this mode of chronic osteomyelitis. There have also been major advances in our understanding of the immune proteome against *S. aureus*, from clinical studies of serum antibodies and media enriched for newly synthesized antibodies (MENSA), which may provide new opportunities for osteomyelitis diagnosis, prognosis, and vaccine development. Finally, novel therapies such as antimicrobial implant coatings and antibiotic impregnated 3D-printed scaffolds represent promising strategies for preventing and managing this devastating disease. Here, we review these recent advances and highlight translational opportunities towards a cure.

Bone Research (2019)7:20 ; https://doi.org/10.1038/s41413-019-0061-z

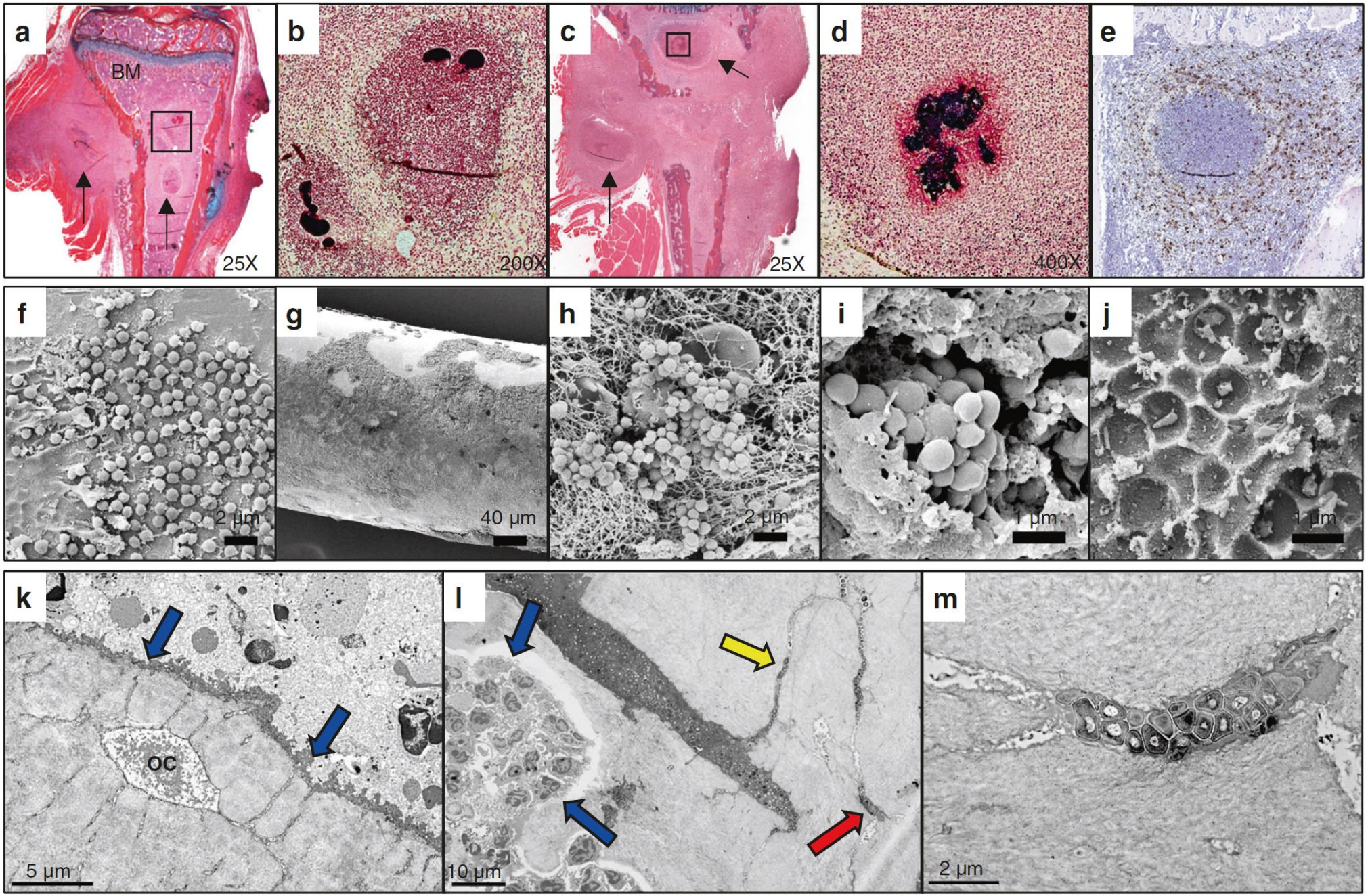
I SACs possono formarsi già dopo 4 gg dall'infezione

Come risposta adattativa allo stress ambientale, i batteri unicellulari spesso formano biofilm per sopravvivere in una comunità multicellulare protetta, in cui sono presenti sottopopolazioni fenotipicamente alterate, che è resistente alla risposta immunitaria dell'ospite e alla terapia antibiotica.

La formazione del biofilme accade in 4 stadi:
(1) Adesione delle cellule batteriche
(2) Proliferazione
(3) Maturazione del biofilm
(4) Distacco

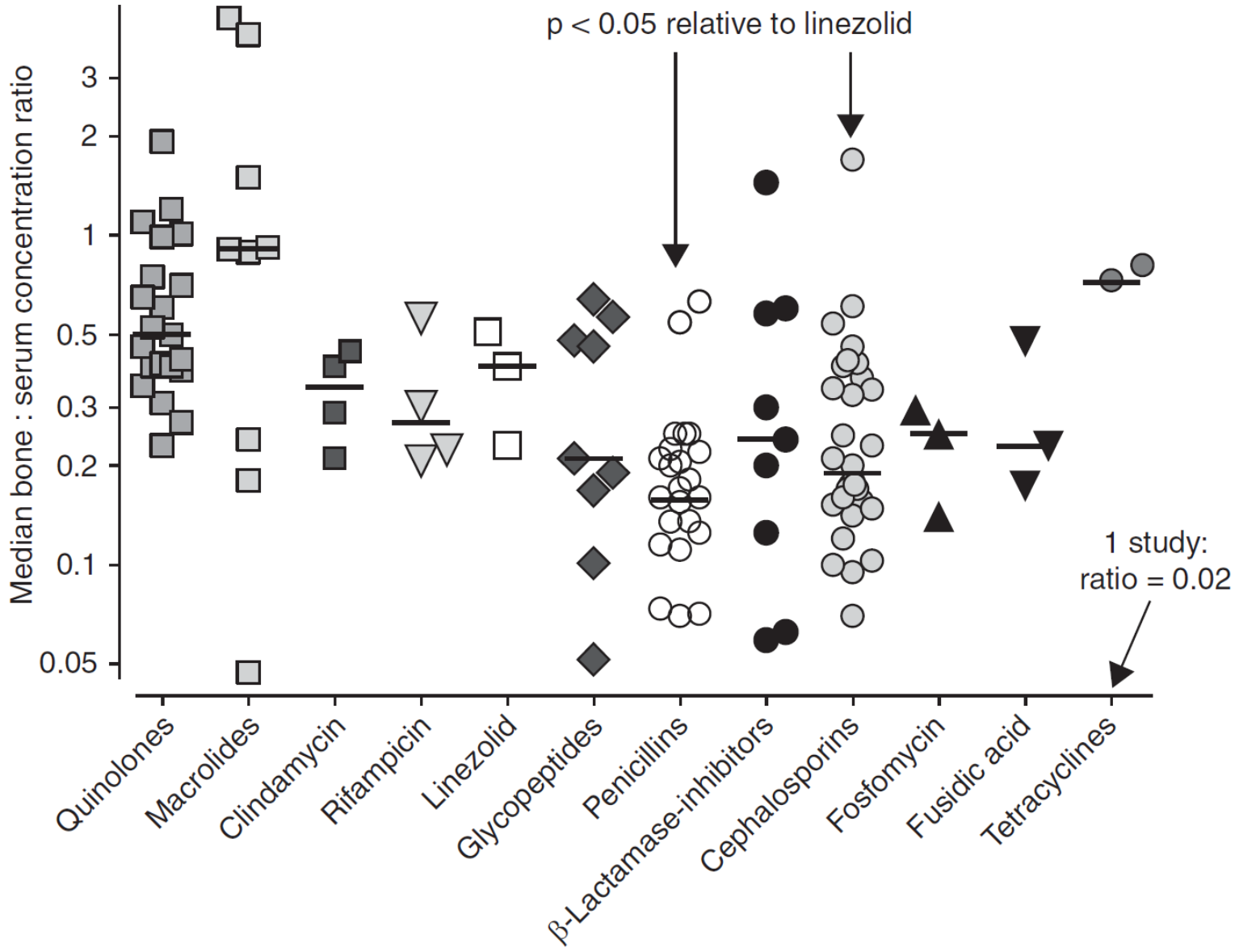
Una volta adese le cellule batteriche proliferanno per espandere la popolazione batterica e iniziare a produrre una matrice di sostanze polmieriche (EPS) per proteggere la comunità multistrato. L'EPS è generalmente composto da polisaccaridi, proteine e acidi nucleici autoprodotti, che racchiudono le cellule batteriche per mediare l'adesione, fornire stabilità meccanica e trattenere nutrienti ed enzimi essenziali.
Man mano che il biofilm matura, diventa una struttura complessa ed eterogenea contenente baccelli protetti di batteri, nonché spazi vuoti e canali intricati per facilitare il trasferimento di nutrienti e ossigeno attraverso la maggior parte del biofilm.
Infine, il distacco o la dispersione del biofilm è un passaggio chiave nella patogenesi, consentendo la metastasi delle cellule batteriche verso altre regioni non colonizzate dell'ospite.
La concentrazione minima eradicante del biofilm (MBEC) deve essere generalmente 100-1000 volte maggiore della concentrazione minima inibente dei batteri planctonici per un dato antibiotico

Il terzo e più recente serbatoio di batteri scoperto nell'osteomielite cronica sembra essere la colonizzazione da parte di *S. aureus* della rete osteocitica-lacuno canalicolare. Nei OLCN i batteri sono circondati dalla densa matrice minerale dell'osso corticale diventando completamente inaccessibili alle cellule immunitarie.
S. aureus potrebbe essere in grado di sopravvivere per decenni all'interno dell'OLCN con una scorta inesauribile di nutrienti, eludendo l'attacco immunitario.


a
BM
25X
b
200X
c
25X
d
400X
e
f
2 µm
g
40 µm
h
2 µm
i
1 µm
j
1 µm
k
OC
5 µm
l
10 µm
m
2 µm

PENETRAZIONE OSSEA

The available data show a larger extent of bone penetration for quinolones, macrolides and linezolid than for b-lactams.
The bone penetration of penicillins and cephalosporins was significantly lower than that of linezolid.



Clin Pharmacokinet 2009; 48 (2)

TABLE II Relative Antibiotic Concentrations and Properties*

Antibiotic	Spectrum of Activity	Average Cancellous Bone Concentration	Average Joint Concentration	Drug-Drug Interactions†	Major Adverse Effects
Flucloxacillin	MSSA	+++	NA	Mild	Nausea, vomiting, diarrhea, jaundice, and hepatitis
Cephalexin	Streptococcus spp., MSSA, enterobacteriaceae	–	+	Mild	Nausea, vomiting, diarrhea, confusion, jaundice, and arthralgia
Clindamycin	Anaerobic gram-positive and gram-negative organisms, including Bacteroides, MRSA, MSSA, *Streptococcus pyogenes,* and *Streptococcus pneumoniae*	+++	++	Mild	Severe diarrhea, metallic taste, rash, and jaundice
Doxycycline	Staphylococcus spp., *Streptococcus pneumoniae, Streptococcus pyogenes,* rickettsial infections, and *Borrelia burgdorferi*	+++	NA	Mild	Ultraviolet sensitivity, tooth discoloration for those who are <8 years old, and pill esophagitis
Trimethoprim-sulfamethoxazole	*Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumonia,* and enterobacteriaceae	++	–	Moderate: warfarin	Hypersensitivity reactions, nephrotoxicity, agranulocytosis, hemolysis, and jaundice
Fluoroquinolones	Staphylococcus spp., Streptococcus spp., enterobacteriaceae, and Pseudomonas (ciprofloxacin and levofloxacin)	+++	+++	Moderate: QT-prolonging medications	QT prolongation, confusion, and tendon inflammation and rupture
Rifampin	Staphylococcus spp.	+++	NA	High: linezolid, clindamycin, warfarin, and estrogen derivatives	Renal failure, hepatic test abnormalities, anemia, nausea, gastroesophageal reflux, and adrenocortical insufficiency
Linezolid	Staphylococcus spp., VRE, and Streptococcus spp.	+	+	Moderate: SSRIs	Diarrhea, headache, anemia, serotonin syndrome, pancytopenia, and optic neuropathy

Review

Antibiotic penetration into bone and joints: An updated review

Abrar K. Thabit*, Dania F. Fatani, Maryam S. Bamakhrama, Ola A. Barnawi,
Lana O. Basudan, Shahad F. Alhejaili

Antibiotics that showed good penetration profiles into bone tissues include amoxicillin, piperacillin/tazobactam, cephalosporins (all four generations), carbapenems (no data for imipenem), aztreonam, aminoglycosides, fluoroquinolones doxycycline, vancomycin, linezolid, daptomycin, clindamycin, tri- methoprim/sulfamethoxazole, fosfomycin, rifampin, dalbavancin, and oritavancin.

Despite the variation in penetration extent, all agents with reported good penetration profiles achieve concentrations that are sufficient for antibacterial activity as demonstrated by the comparison with the MIC90 or the MIC breakpoints of various organisms implicated in bone and joint infections.

A.K. Thabit et al./International Journal of Infectious Diseases 81 (2019) 128–136

PATOGENI MDR

80% delle PJI sono causate da batteri GRAM+
e la presenza di patogeni MDR o DDT correla con un aumentato rischio di fallimento

MRSA

- Vancomicina
- Linezolid
- Daptomicina
- Dalbanvancina o Oritavancina
- +- fosfomicina

Nello switch a tp orale in base alla S:

- TMP/SMX
- Doxiciclina
- Clindamicina
- chinolonici

CONS

- Anche quando OXA-S potrebbero esserci delle sottopopolazioni meticillino R, quindi specie nelle DAIR potrebbe essere razionali trattarli sempre come OXA-R

Enterococchi

- Nei Vanco- S la monoterapia con beta-lattamici o vancomicina può essere batteriostatica, l' aggiunta di un aminoglicoside potrebbe migliorare l'outcome determinando un effetto battericida
- Nei VRE daptomicina, linezolid, tigeciclina, dalbavancina, oritavancina +- fosfosmicina

Valutare sempre l'associazione con rifampicina, il dosaggio è molto dibattutto (<10 mg/kg o 10-20 mg/Kg)

In vitro activity of dalbavancin against biofilms of staphylococci isolated from prosthetic joint infections

Javier Fernández [a,b,c], Kerryl E. Greenwood-Quaintance [a], Robin Patel [a,d,*]

[a] *Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA*
[b] *Department of Functional Biology, Section of Microbiology, University of Oviedo, Oviedo, Spain*
[c] *Service of Microbiology, Hospital Universitario Central de Asturias, Oviedo, Spain*
[d] *Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, MN, USA*

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ABSTRACT

The *in vitro* activity of dalbavancin was tested against biofilms of 171 staphylococci associated with prosthetic joint infection. Dalbavancin minimum biofilm bactericidal concentration (MBBC) values were: $MBBC_{50}$ for *Staphylococcus aureus* and *Staphylococcus epidermidis*, 1 μg/mL; $MBBC_{90}$ for *S. aureus*, 2 μg/mL; $MBBC_{90}$ for *S. epidermidis*, 4 μg/mL.

In vitro time-kill kinetics of dalbavancin against *Staphylococcus* spp. biofilms over prolonged exposure times

Vincenzo Di Pilato [a], Federica Ceccherini [b], Samanta Sennati [b], Federico D'Agostino [b], Fabio Arena [b,#], Noemi D'Atanasio [c], Francesco Paolo Di Giorgio [c], Serena Tongiani [c], Lucia Pallecchi [b,*] and Gian Maria Rossolini [a,d,*]

Dalbavancin treatment for prosthetic joint infections in real-life: a national cohort study and literature review

Morgan Matt[a], Clara Duran[a], Johan Courjon[b], Romain Lotte[c], Vincent Le Moing[d], Boris Monnin[d], Patricia Pavese[e], Pascal Chavanet[f], Lydie Khatchatourian[g], Pierre Tattevin[h], Vincent Cattoir[i], Catherine Lechiche[j], Gabriella Illes[k], Flore Lacassin-Beller[k], Eric Senneville[l], Aurélien Dinh[a,*], on behalf of the Dalbavancin French Study Group

A B S T R A C T

Objectives: Dalbavancin is a long-lasting lipoglycopeptide active against Gram-positive bacteria, especially methicillin-resistant staphylococci. Few data are available on dalbavancin use for treatment of prosthetic joint infections (PJIs). We describe a cohort of patients treated for PJI with dalbavancin and review the literature regarding this condition.

Methods: All adult patients with PJI from the French dalbavancin national cohort from 1 June 2017 to 1 January 2019 were included. We collected clinical and microbiological characteristics and outcome through a standardised questionnaire. Clinical cure was defined as absence of clinical signs of infection at last visit. Failure was a composite criterion defined by persistence or reappearance of signs of infection, and/or switch to suppressive antibiotic treatment and/or death from infection. The literature review was performed using PubMed.

Results: Seventeen patients were included. Bacteria were identified in 16 cases: *Staphylococcus aureus* ($n = 10$), including methicillin-resistant *S. aureus* ($n = 1$); and coagulase-negative staphylococci ($n = 10$), including methicillin-resistant *Staphylococcus epidermidis* ($n = 4$). Sixteen patients (94.1%) had received antibiotic therapy prior to dalbavancin use (mean of 2.2 ± 1.3 lines). Clinical cure was achieved in 8/17 patients after a median follow-up of 299.0 (IQR 97.0–476.0) days. We reviewed all cases of PJI treated with dalbavancin available in the literature and the overall clinical cure was estimated at 73.1%.

Conclusion: Our study and literature data suggest that use of dalbavancin in PJI could be considered, even as salvage therapy. Dalbavancin appears to be a safe and easy treatment for patients with staphylococcal PJIs.

Journal of Global Antimicrobial Resistance 25 (2021) 341–345

antibiotics

MDPI

Article

Tolerance of Prolonged Oral Tedizolid for Prosthetic Joint Infections: Results of a Multicentre Prospective Study

Eric Senneville [1,2,3,*], Aurélien Dinh [4,5], Tristan Ferry [6,7], Eric Beltrand [3,8], Nicolas Blondiaux [3,9] and Olivier Robineau [1,2,3]

Abstract: Objectives: Data on clinical and biological tolerance of tedizolid (TZD) prolonged therapy are lacking. Methods: We conducted a prospective multicentre study including patients with prosthetic joint infections (PJIs) who were treated for at least 6 weeks but not more than 12 weeks. Results: Thirty-three adult patients of mean age 73.3 ± 10.5 years, with PJI including hip (n = 19), knee (n = 13) and shoulder (n = 1) were included. All patients were operated, with retention of the infected implants and one/two stage-replacements in 11 (33.3%) and 17/5 (51.5%/15.2%), respectively. Staphylococci and enterococci were the most prevalent bacteria identified. The mean duration of TZD therapy was 8.0 ± 3.27 weeks (6–12). TZD was associated with another antibiotic in 18 patients (54.5%), including rifampicin in 16 cases (48.5). Six patients (18.2%) had to stop TZD therapy prematurely because of intolerance which was potentially attributable to TZD (n = 2), early failure of PJI treatment (n = 2) or severe anaemia due to bleeding (n = 2). Regarding compliance with TZD therapy, no cases of two or more omissions of medication intake were recorded during the whole TZD treatment duration. Conclusions: These results suggest good compliance and a favourable safety profile of TZD, providing evidence of the potential benefit of the use of this agent for the antibiotic treatment of PJIs.

Antibiotics **2021**, *10*, 4. https://dx.doi.org/10.3390/antibiotics10010004

Case report

Successful treatment of a prosthetic hip infection due to *Enterococcus faecalis* with sequential dosing of oritavancin and prosthesis preservation without prosthetic joint surgical manipulation

Jullian P. Nguyen[a], Brian X. Contreras[a], Miguel Sierra-Hoffman[b], Kim Saddler[c], Mark L. Stevens[d], Miriams T. Castro-Lainez[e], Brett Knox[f], Rafael J. Deliz[g,*]

A B S T R A C T

A patient with a prosthetic joint infection (PJI) complicated with deep surgical site infection due to vancomycin-susceptible *Enterococcus faecalis. The* initial treatment consisted of 10 days with daptomycin plus ampicillin. The hip prosthesis was retained and salvaged with six outpatient sequential doses of oritavancin 1200 mg every seven days without intra-articular irrigation or other surgical interventions. The patient was ambulating independently without symptoms after ten months of the last treatment of oritavancin.

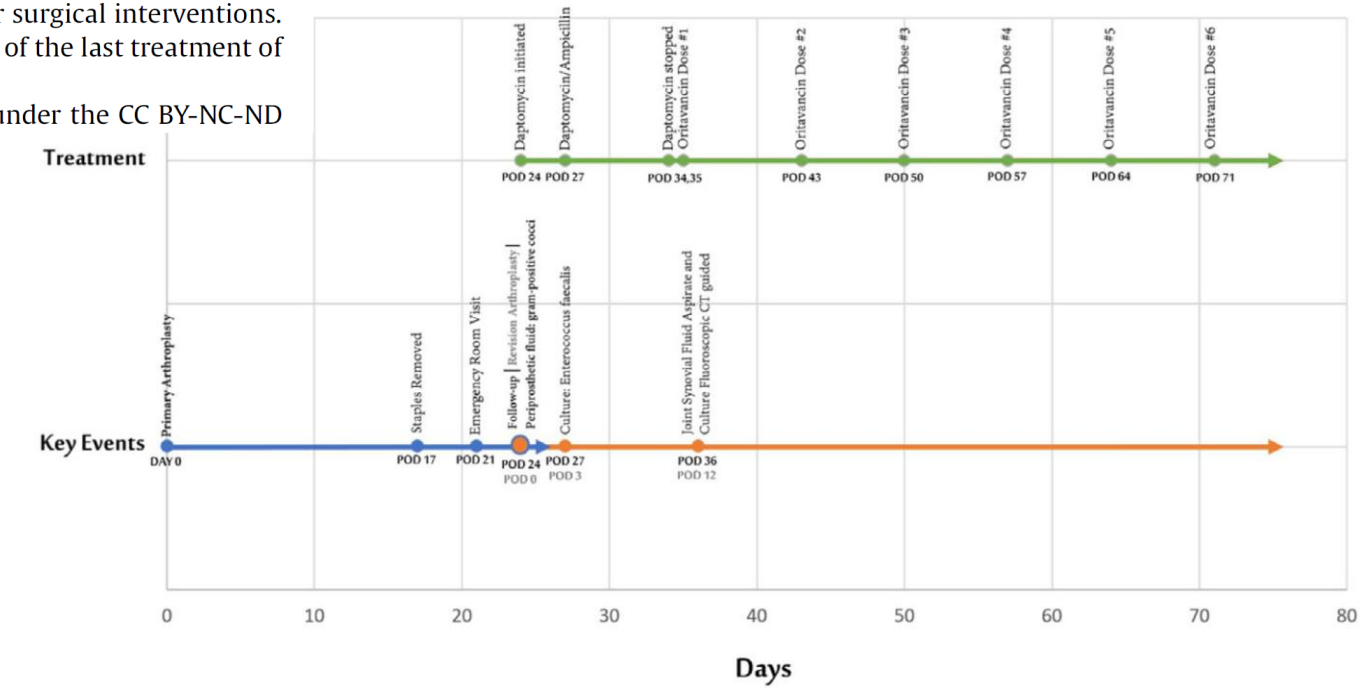

Fig. 2. Timeline of Events.

Treatment of Acute Osteomyelitis with Once-Weekly Oritavancin: A Two-Year, Multicenter, Retrospective Study

Nicholas W. Van Hise[1] · Vishnu Chundi[1] · Vishal Didwania[1] · Michael Anderson[1] · David McKinsey[2] · Ingrid Roig[3] · Akhilesh Sharma[4] · Russell M. Petrak[1]

Abstract

Background Acute osteomyelitis is typically caused by Gram-positive pathogens, commonly antibiotic-resistant *Staphylococcus* species. Standard antibiotic treatment is challenging due to required multiple daily doses, therapeutic drug monitoring, and parenteral administration for at least 4 weeks. Oritavancin is a long-acting lipoglycopeptide antibiotic approved as a single 1200 mg dose for the treatment of adult patients with acute bacterial skin and skin structure infections.

Objective To characterize the real-world use, efficacy, and safety of oritavancin in adult patients with acute osteomyelitis.

Methods This was a 2-year, multicenter, retrospective, descriptive study of patients treated for acute osteomyelitis with weekly doses of oritavancin. End of therapy evaluation (ETE) was defined as evaluation at 7–10 days after the last dose of oritavancin, and post-therapy assessment (PTE) was at 3 months and 6 months. At ETE and PTE, patients were interviewed via telephone for clinical outcomes, using a standard questionnaire. Electronic medical record review was also conducted.

Results 134 patients were treated with oritavancin for acute osteomyelitis across 20 different Metro Infectious Disease Consultants infusion centers in six states. Of total positive cultures, 71.9% (92/128) were methicillin-resistant *Staphylococcus aureus* (MRSA) from deep wounds, bone, or joint culture; an additional nine (6.7%) of 134 patients presented with concomitant MRSA bacteremia. Oritavancin was administered via intravenous catheter; patients received an initial treatment of 1200 mg and then 800 mg weekly thereafter for a total number of doses of four ($n = 118$) or five ($n = 16$). 118 patients (88.1%) of the baseline 134 patients achieved clinical success at the ETE timepoint. 130 patients were available for PTE at 3 months and 6 months. Overall, relapse or persistent infection was diagnosed in 13/134 (9.7%) patients. Nine (6.7%) of 134 patients were admitted to the hospital during the follow-up period but none for osteomyelitis. Adverse events were reported in five (3.7%) patients including hypoglycemia-related symptoms (three patients), tachycardia (one patient), and tachycardia with chest pain (one patient). None of these patients were hospitalized due to adverse events, and all patients eventually finished their treatment regimens.

Conclusion This is the largest real-world clinical study of adult patients treated with oritavancin for acute osteomyelitis. Use of oritavancin for acute osteomyelitis infection resulted in a high rate of positive clinical outcomes and a low incidence of adverse events, thereby providing potential for a convenient, effective, and safe therapeutic option. Future prospective and comparative studies are needed to validate these findings.

Drugs - Real World Outcomes (2020) 7 (Suppl 1):S41–S45

The role of fosfomycin in osteoarticular infection

ABSTRACT

Osteoarticular infections include septic arthritis and osteomyelitis, with Gram-positive microorganisms isolated most frequently. In recent years, there has been an increase in the number of resistant strains in this type of infection, which complicates the treatment. Fosfomycin is active against a large percentage of Gram-positive and Gram-negative pathogens, including multidrug-resistant strains, and its properties include low protein binding, low molecular weight and good bone dissemination. In this article, we discuss fosfomycin's activity *in vitro*, its pharmacokinetic and pharmacodynamic parameters of interest in osteoarticular infections, the experimental models of osteomyelitis and foreign body infection and the clinical experience with these types of infections.

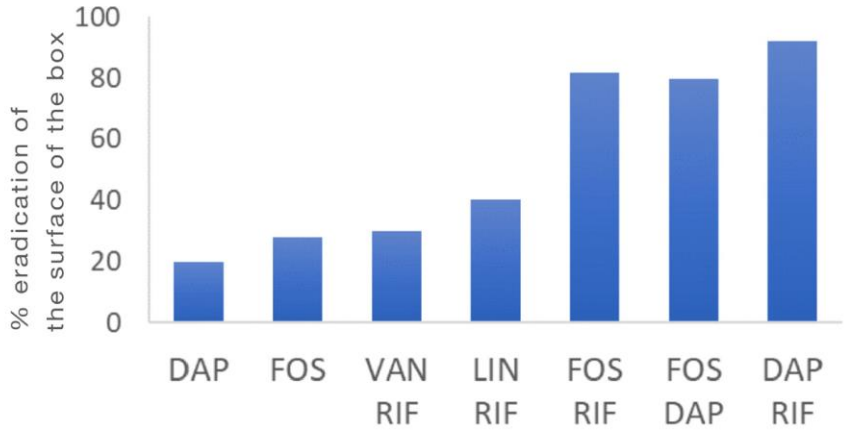

Figure 1 | Percentage eradication of an methicillin-resistant *Staphylococcus aureus* biofilm in the animal model of foreign body infection [32-38].

DAP, daptomycin; FOS, fosfomycin; VAN, vancomycin; RIF, rifampicin; LIN, linezolid.

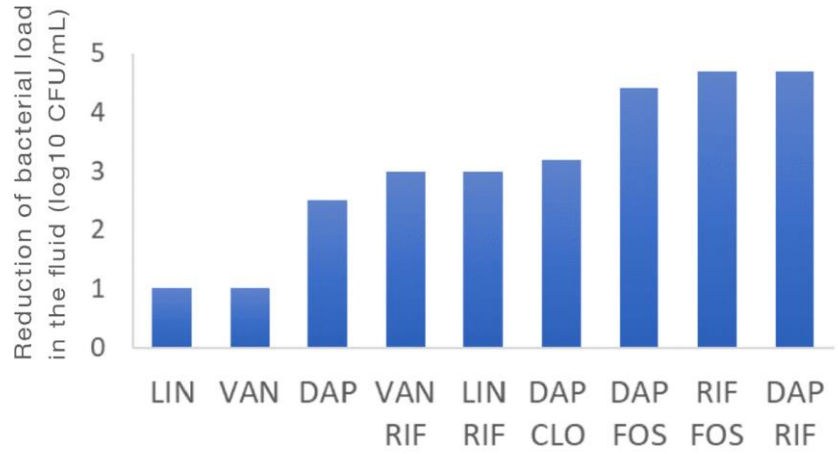

Figure 2 | Decrease in bacterial load in the interior of the box of the foreign body animal model by methicillin-resistant *Staphylococcus aureus* [32-38].

CLO, cloxacillin; DAP, daptomycin; FOS, fosfomycin; LIN, linezolid; RIF, rifampicin; VAN, vancomycin.

Compassionate use of cefiderocol for carbapenem-resistant *Acinetobacter baumannii* prosthetic joint infection

Diana A. Mabayoje[1]*, Caoimhe NicFhogartaigh[1], Benny P. Cherian[1], Mei Gie Meiqi Tan[2] and David W. Wareham [1,2]

Background: Cefiderocol is a recently licensed novel siderophore-conjugated cephalosporin stable to hydrolysis by serine and MBLs. It has been successfully used to treat Enterobacterales infections and is approved for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

Objectives: To describe the compassionate use of cefiderocol and clinical outcome in a case of prosthetic joint infection due to MDR *Acinetobacter baumannii*.

Patients and methods: This case study follows a 66-year-old woman who sustained an open fracture of the left distal humerus in Pakistan. She underwent open reduction and internal fixation and on return to the UK presented to hospital with a discharging surgical wound.

Results: Debridement of her wound cultured NDM carbapenemase-producing *A. baumannii* susceptible to colistin, tobramycin and tigecycline only. She developed vomiting with acute kidney injury with colistin and tigecycline. Antimicrobial efficacy of cefiderocol was predicted from *in vitro* and *in vivo* susceptibility tests. A successful request was made to Shionogi for compassionate use of cefiderocol, which was added to tigecycline. Cefiderocol was well tolerated with no toxicity and improved renal function. In total she received 25 days of cefiderocol and continued on tigecycline for a further 6 weeks in the community. She has well-healed wounds and good range of elbow movement.

Conclusions: Cefiderocol's novel mode of cell entry is effective against MDR Gram-negative bacteria with reduced toxicity compared with other last line antibiotics. Our case demonstrates that cefiderocol may be useful as therapy for patients with limited treatment options due to antimicrobial resistance. **The prescribing information for cefiderocol is available at: https://shionogi-eu-content.com/gb/fetcroja/pi.**

J Antimicrob Chemother 2021; **3** Suppl 1: i21–i24

Case Report

Prosthetic Joint Infection from Carbapenemase-Resistant *Klebsiella pneumoniae* Successfully Treated with Ceftazidime-Avibactam

A. Schimmenti,[1] E. Brunetti,[1,2] E. Seminari,[2] B. Mariani,[3] P. Cambieri,[3] and P. Orsolini[2,4]

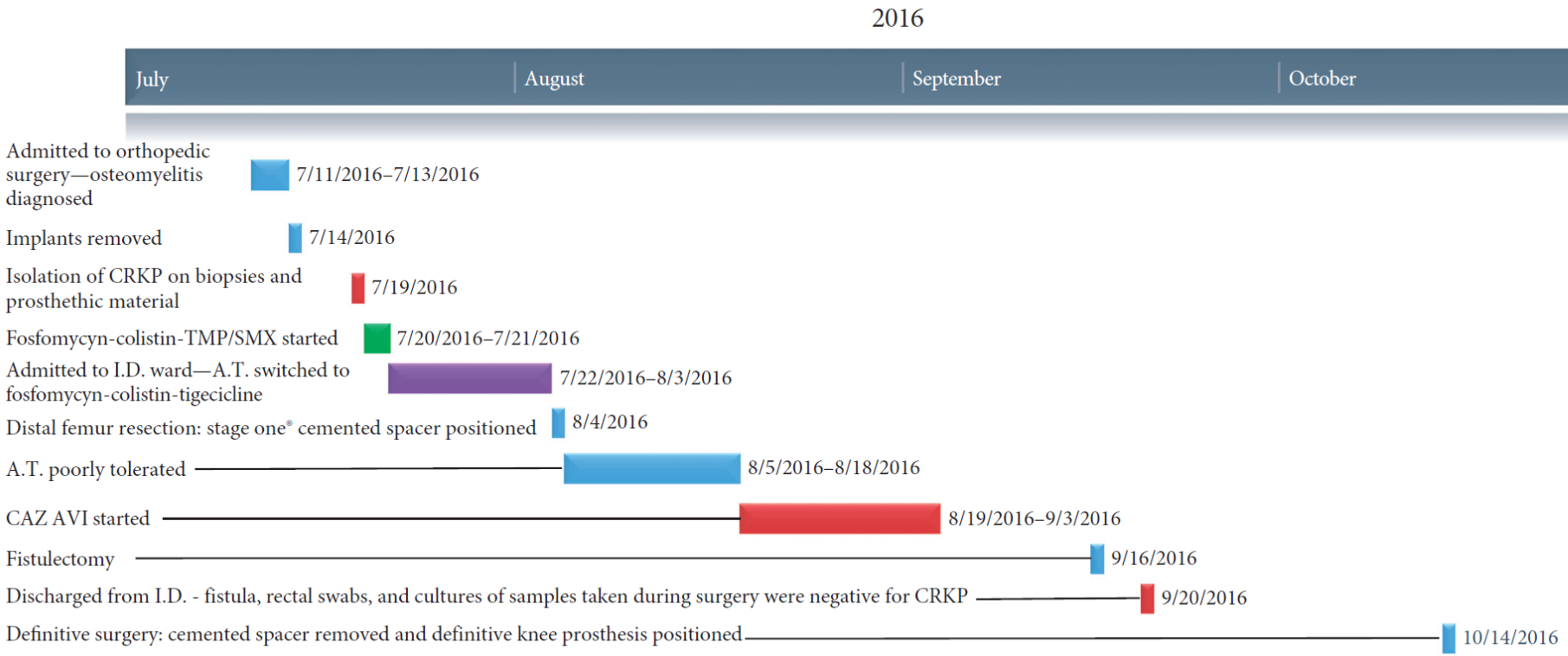

Figure 4: Timeline of antibiotic and surgical treatments.

Prosthetic knee infection by resistant bacteria: the worst-case scenario

Michele Vasso[1] · Alfredo Schiavone Panni[1] · Ivan De Martino[2] · Giorgio Gasparini[3]

Conclusions

Two-stage reimplantation in most cases remains a viable option for the treatment of TKA infections by resistant bacteria (mainly MRSA and MRSE: 10 % failure rate).

However, both the surgeon and the patient should consider the higher possibility of failure when the infection is caused by multidrug highly resistant organisms (mainly VRE, MDR *Acinetobacter Baumannii* and MDR *Pseudomonas aeruginosa*: 33 % failure rate). Finally, loss of the prosthesis and, in some cases, of the limb (10 % in this study) remains a concrete possibility when resistant organisms are involved.

Knee Surg Sports Traumatol Arthrosc

TIMING DELLA DURATA DELLA TERAPIA

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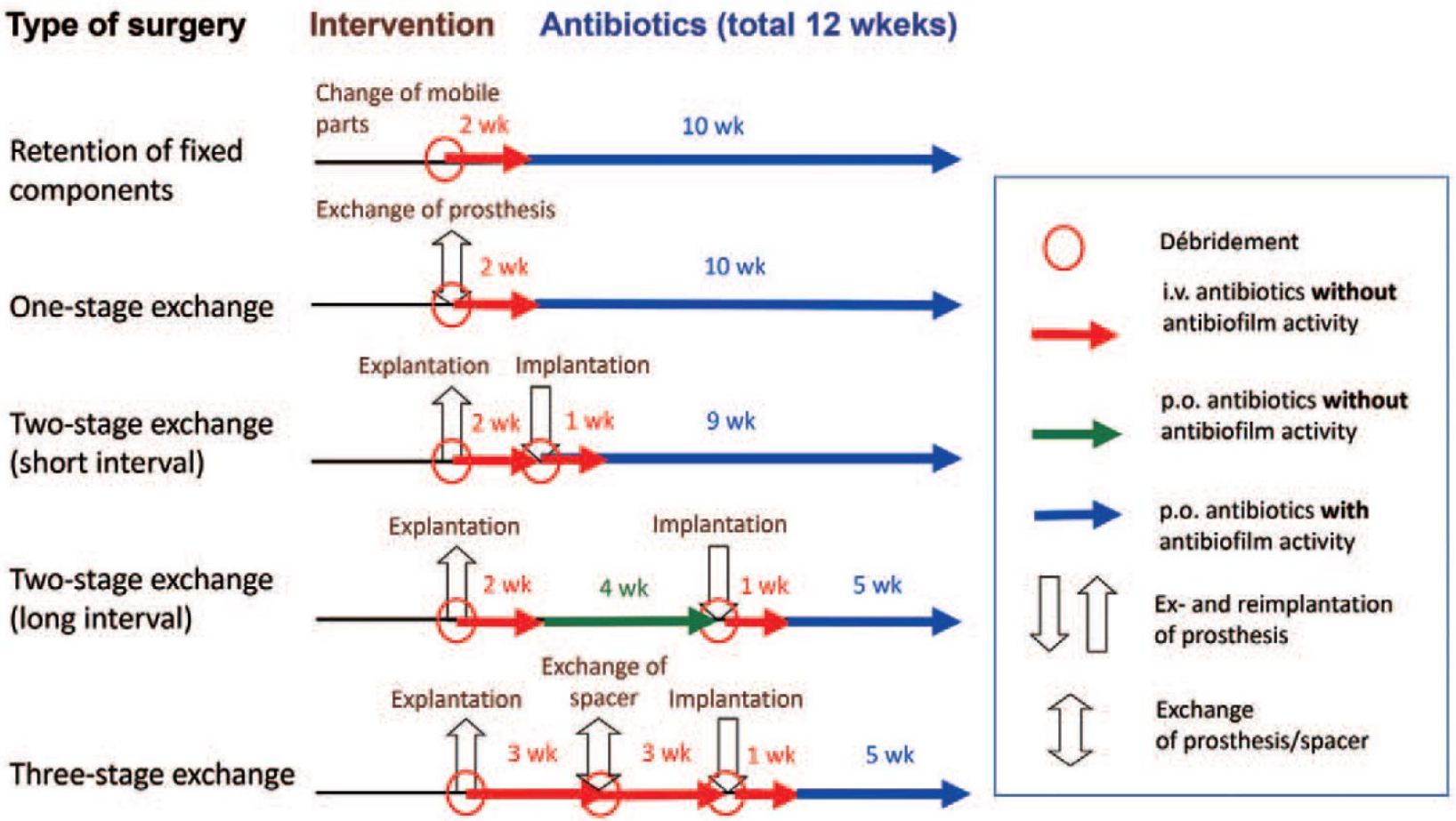
Hip & Pelvis

Management of Periprosthetic Joint Infection

Cheng Li, MD, Nora Renz, MD, Andrej Trampuz, MD

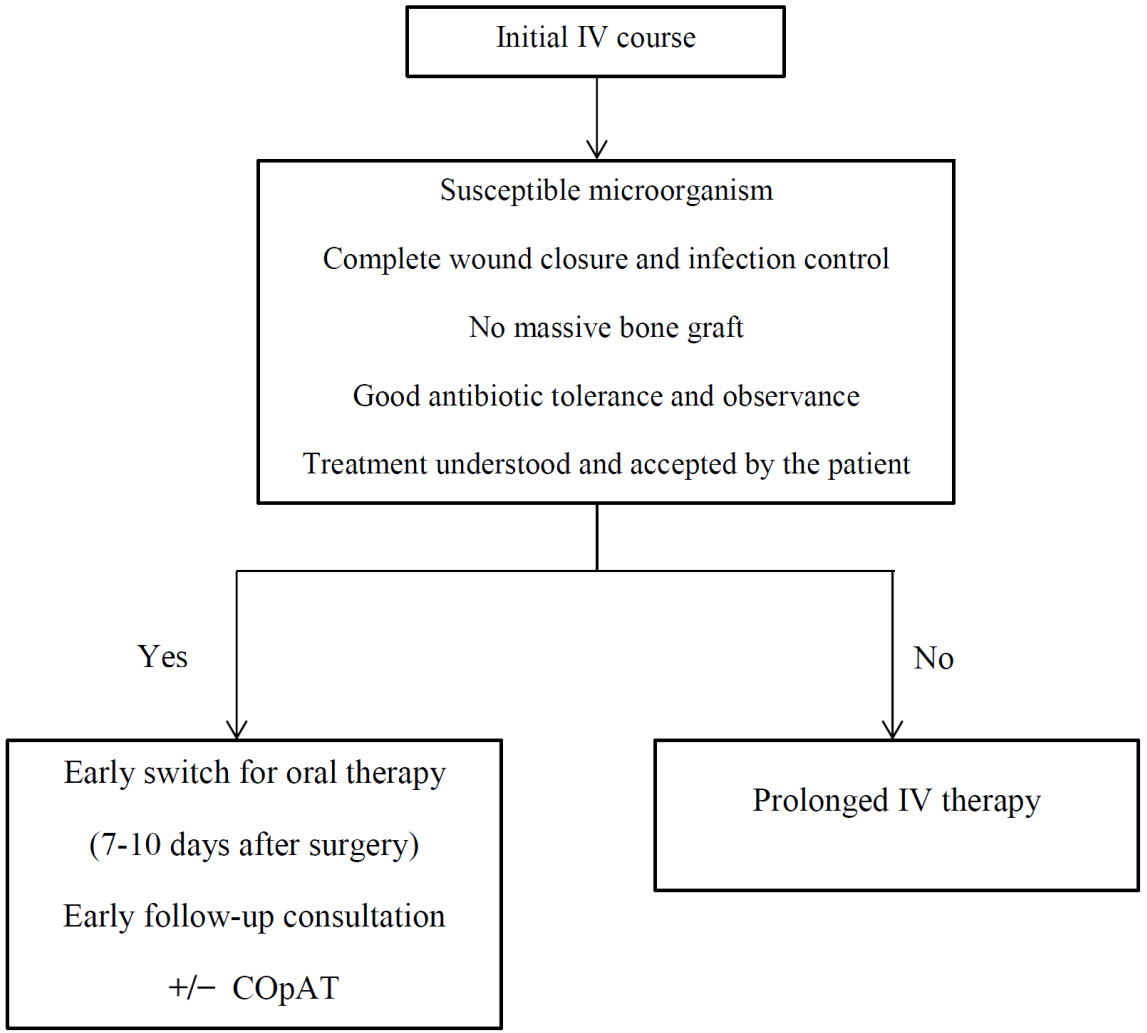
Center for Musculoskeletal Surgery (CMSC), Charité-Universitätsmedizin Berlin,
Corporate Member of Freie Universi
and Berlin Institute o

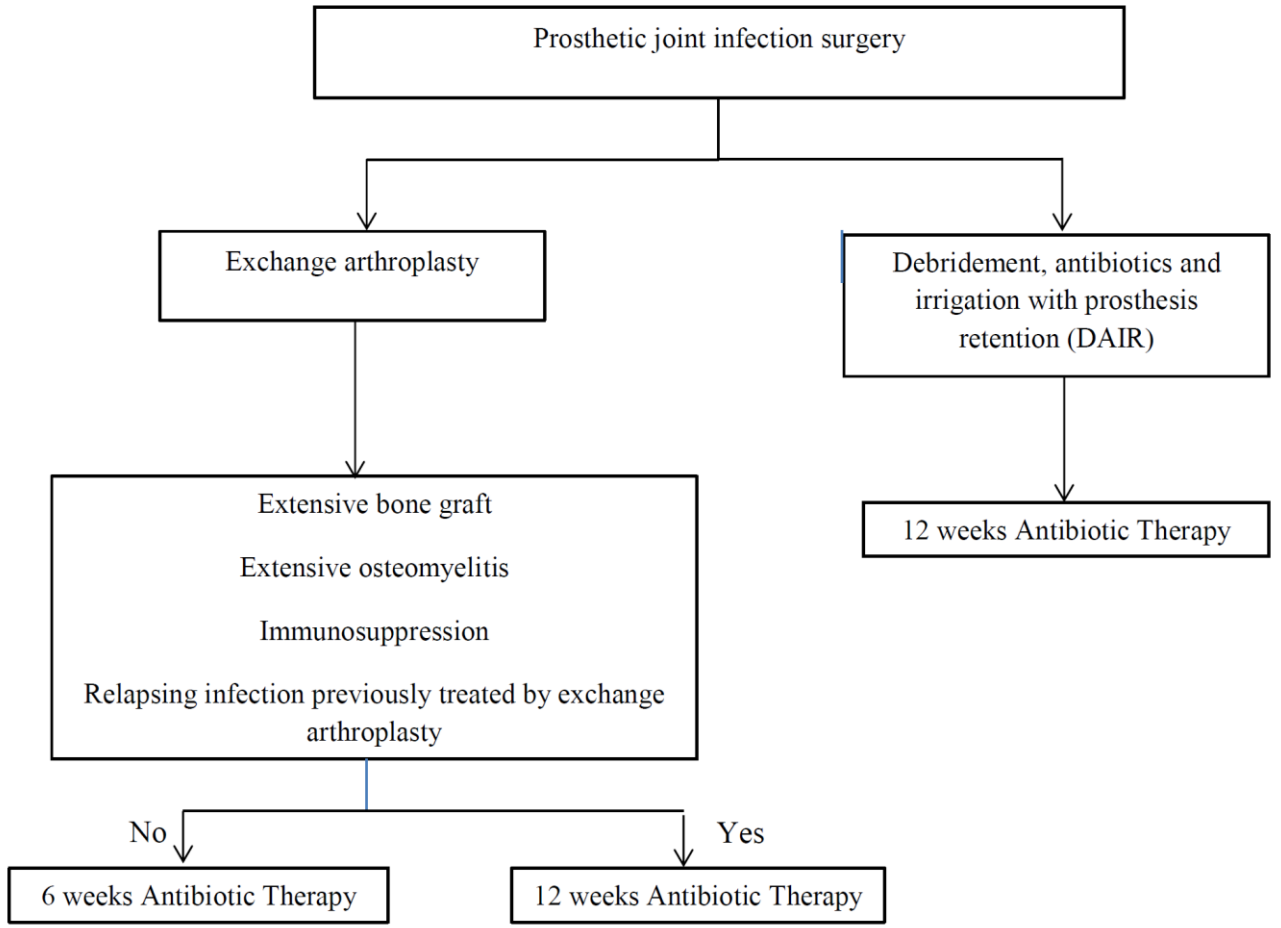


Review

Antibiotic Therapy for Prosthetic Joint Infections: An Overview

Benjamin Le Vavasseur [1,2] and Valérie Zeller [1,2,*]





Antibiotics **2022**, *11*, 486. https://doi.org/10.3390/antibiotics11040486

Oral versus Intravenous Antibiotics for Bone and Joint Infection

Abstract

Background—The management of complex orthopedic infections usually includes a prolonged course of intravenous antibiotic agents. We investigated whether oral antibiotic therapy is noninferior to intravenous antibiotic therapy for this indication.

Methods—We enrolled adults who were being treated for bone or joint infection at 26 U.K. centers. Within 7 days after surgery (or, if the infection was being managed without surgery, within 7 days after the start of antibiotic treatment), participants were randomly assigned to receive either intravenous or oral antibiotics to complete the first 6 weeks of therapy. Follow-on oral antibiotics were permitted in both groups. The primary end point was definitive treatment failure within 1 year after randomization. In the analysis of the risk of the primary end point, the noninferiority margin was 7.5 percentage points.

Results—Among the 1054 participants (527 in each group), end-point data were available for 1015 (96.3%). Treatment failure occurred in 74 of 506 participants (14.6%) in the intravenous group and 67 of 509 participants (13.2%) in the oral group. Missing end-point data (39 participants, 3.7%) were imputed. The intention-to-treat analysis showed a difference in the risk of definitive treatment failure (oral group vs. intravenous group) of −1.4 percentage points (90% confidence interval [CI], −4.9 to 2.2; 95% CI, −5.6 to 2.9), indicating noninferiority. Complete-case, per-protocol, and sensitivity analyses supported this result. The between-group difference in the incidence of serious adverse events was not significant (146 of 527 participants [27.7%] in the intravenous group and 138 of 527 [26.2%] in the oral group; P = 0.58). Catheter complications, analyzed as a secondary end point, were more common in the intravenous group (9.4% vs. 1.0%).

Conclusions—Oral antibiotic therapy was noninferior to intravenous antibiotic therapy when used during the first 6 weeks for complex orthopedic infection, as assessed by treatment failure at 1 year. (Funded by the National Institute for Health Research; OVIVA Current Controlled Trials number, ISRCTN91566927.)

N Engl J Med. 2019 January 31; 380(5): 425–436. doi:10.1056/NEJMoa1710926.

THE KNEE SOCIETY

2020 Mark Coventry Award: Microorganism-directed oral antibiotics reduce the rate of failure due to further infection after two-stage revision hip or knee arthroplasty for chronic infection: a multicentre randomized controlled trial at a minimum of two years

J. Yang,
J. Parvizi,
E. N. Hansen,
C. N. Culvern,
J. C. Segreti,
T. Tan,
C. W. Hartman,
S. M. Sporer,
C. J. Della Valle,
The Knee Society Research Group

Rush University Medical Center, Chicago, Illinois, USA

Aims

The aim of this study was to determine if a three-month course of microorganism-directed oral antibiotics reduces the rate of failure due to further infection following two-stage revision for chronic prosthetic joint infection (PJI) of the hip and knee.

Methods

A total of 185 patients undergoing a two-stage revision in seven different centres were prospectively enrolled. Of these patients, 93 were randomized to receive microorganism-directed oral antibiotics for three months following reimplantation; 88 were randomized to receive no antibiotics, and four were withdrawn before randomization. Of the 181 randomized patients, 28 were lost to follow-up, six died before two years follow-up, and five with culture negative infections were excluded. The remaining 142 patients were followed for a mean of 3.3 years (2.0 to 7.6) with failure due to a further infection as the primary endpoint. Patients who were treated with antibiotics were also assessed for their adherence to the medication regime and for side effects to antibiotics.

Results

Nine of 72 patients (12.5%) who received antibiotics failed due to further infection compared with 20 of 70 patients (28.6%) who did not receive antibiotics ($p = 0.012$). Five patients (6.9%) in the treatment group experienced adverse effects related to the administered antibiotics severe enough to warrant discontinuation.

Conclusion

This multicentre randomized controlled trial showed that a three-month course of microorganism-directed, oral antibiotics significantly reduced the rate of failure due to further infection following a two-stage revision of total hip or knee arthroplasty for chronic PJI.

Cite this article: *Bone Joint J* 2020;102-B(6 Supple A):3–9.

ALTRE TERAPIE

Review

Past and Future of Phage Therapy and Phage-Derived Proteins in Patients with Bone and Joint Infection

Tristan Ferry [1,2,3,4,*], Camille Kolenda [1,2,3,4], Thomas Briot [1], Aubin Souche [1,2,3,4], Sébastien Lustig [1,2,3], Jérôme Josse [1,2,3,4], Cécile Batailler [1,2,3], Fabrice Pirot [1,2,5], Mathieu Medina [1], Gilles Leboucher [1], Frédéric Laurent [1,2,3,4], on behalf of the Lyon BJI Study Group [†] and on behalf of the PHAGE*in*LYON Study Group [‡]

Viruses **2021**, *13*, 2414. https://doi.org/10.3390/v13122414

Phage Activity against Planktonic and Biofilm *Staphylococcus aureus* Periprosthetic Joint Infection Isolates

Katherine M. C. Totten,[a,b] Robin Patel[a,c]

January 2022 Volume 66 Issue 1 e01879-21

The Rationale for Using Bacteriophage to Treat and Prevent Periprosthetic Joint Infections

Jonas D. Van Belleghem[1†], Robert Manasherob[2†], Ryszard Międzybrodzki[3], Paweł Rogóż[3], Andrzej Górski[3], Gina A. Suh[4], Paul L. Bollyky[1] and Derek F. Amanatullah[2]*

[1] Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University, Stanford, CA, United States, [2] Department of Orthopaedic Surgery, Stanford University, Stanford, CA, United States, [3] Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wrocław, Poland, [4] Mayo Clinic, Rochester, MN, United States

Prosthetic joint infection (PJI) is a devastating complication after a joint replacement. PJI and its treatment have a high monetary cost, morbidity, and mortality. The lack of success treating PJI with conventional antibiotics alone is related to the presence of bacterial biofilm on medical implants. Consequently, surgical removal of the implant and prolonged intravenous antibiotics to eradicate the infection are necessary prior to re-implanting a new prosthetic joint. Growing clinical data shows that bacterial predators, called bacteriophages (phages), could be an alternative treatment strategy or prophylactic approach for PJI. Phages could further be exploited to degrade biofilms, making bacteria more susceptible to antibiotics and enabling potential combinatorial therapies. Emerging research suggests that phages may also directly interact with the innate immune response. Phage therapy may play an important, and currently understudied, role in the clearance of PJI, and has the potential to treat thousands of patients who would either have to undergo revision surgery to attempt to clear an infections, take antibiotics for a prolonged period to try and suppress the re-emerging infection, or potentially risk losing a limb.

doi: 10.3389/fmicb.2020.591021

BACTERIOPHAGE THERAPY AS A TREATMENT STRATEGY FOR ORTHOPAEDIC-DEVICE-RELATED INFECTIONS: WHERE DO WE STAND?

J. Onsea[1,2,*], J. Wagemans[3], J.P. Pirnay[4], M. Di Luca[5], M. Gonzalez-Moreno[6], R. Lavigne[3], A. Trampuz[6], T.F. Moriarty[7] and W-J. Metsemakers[1,2]

Abstract

Antibiotic resistance represents a key challenge of the 21st century. Since the pipeline of new antibiotics in development is limited, the introduction of alternative antimicrobial strategies is urgently required.

Bacteriophage therapy, the use of bacterial viruses to selectively kill bacterial pathogens, is re-emerging as a potential strategy to tackle difficult-to-treat and multidrug-resistant pathogens. The last decade has seen a surge in scientific investigation into bacteriophage therapy, including targeting orthopaedic-device-related infections (ODRIs) in several successful case studies. However, pharmacological data, knowledge on the interplay with the immune system and, especially in ODRIs, the optimal local application strategy and treatment outcomes remain scarce.

The present review reports the state-of-the-art in bacteriophage therapy in ODRIs and addresses the hurdles in establishing bacteriophage therapy under good clinical practice guidelines. These hurdles include a lack of data concerning bacteriophage production, processing, administration and dosing, as well as follow-up clinical monitoring reports. To overcome these challenges, an integrated clinical approach is required, supported by comprehensive legislature to enable expansive and correctly implemented clinical trials.

European Cells and Materials Vol. 39 2020 (pages 193-210) DOI: 10.22203/eCM.v039a13

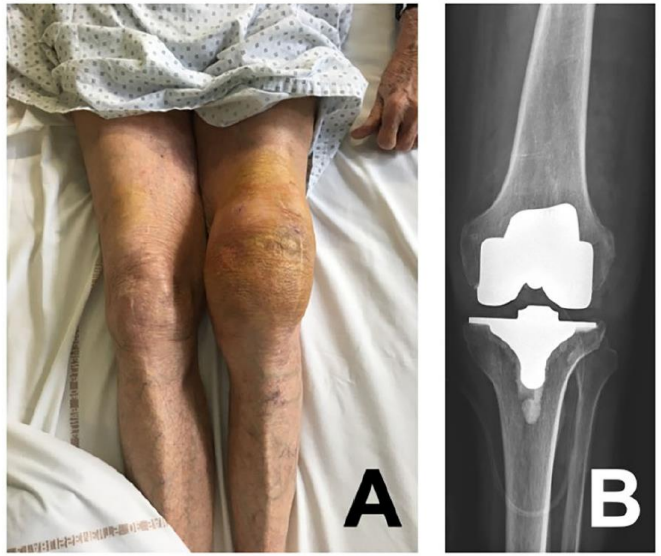
Treatment studies					
Yilmaz *et al.*, 2013	Rat model of implant-associated osteomyelitis	4 groups: - phage - antibiotics - phage + antibiotics - negative control	MRSA/ *P. aeruginosa*	Sb-1/ PAT14 Local injection on three consecutive days	Combination therapy resulted in the highest bacterial killing rate across all groups
Kishor *et al.*, 2016	Rabbit model of osteomyelitis	3 groups: - acute osteomyelitis: phage therapy start after 16 d - chronic osteomyelitis: phage therapy start after 6 weeks - positive control	MRSA	Cocktail with SA-BHU1, SA-BHU2, SA-BHU15, SA-BHU21, SA-BHU37, SA-BHU47	Phage therapy succeeded in eradicating the infection
Cobb *et al.*, 2019	Rat model of implant-associated osteomyelitis and soft tissue infection	- 4 groups: - alginate hydrogel loaded with phage - alginate hydrogel loaded with phosphomycin - alginate hydrogel loaded with phage and phosphomycin - positive control (empty alginate hydrogel)	*S. aureus*	ΦSaBov-CRISPR/Cas9	Phage therapy and the combination of phage therapy and antibiotics resulted in a significant reduction in the bacterial load in the soft tissue, not in bone. A high dose of phosphomycin (3 g) could reduce the bacterial load in bone

Reference	Sample size	Patient characteristics	Intervention	Outcome
Lang *et al.*, 1979	7	PJI (n = 2) OM (n = 1) Septic arthritis (n = 1) Spinal infection (n = 1) FRI (n = 2)	Phages adapted to isolated strains Administration either topical or by injection through a draining system. Some cases received combination treatment with antibiotics	5/7 treated Recurrence of spinal infection and one FRI
Kutateladze and Adamia, 2010	120	Patients with staphylococcal OM or arthritis	Three groups: - antibiotics (n = 60) - phage monotherapy (n = 9) - phage + antibiotics (n = 51) Administration of Eliava staphylococcal phage preparation topically or intravenously	100 % success rate in all groups
Slopek *et al.*, 1987	100	Purulent arthritis and myositis (n = 19) OM of the long bones (n = 40) FRI (n = 41)	Administration locally and/or orally Some cases received combination treatment with antibiotics	Success rates: - purulent arthritis and myositis: 89.5 % - OM of the long bones: 95 % - FRI: 90.2 %
Weber-Dabrowska *et al.*, 2000	81	OM of the long bones (n = 40) FRI (n = 41)	Administration locally and/or orally Unclear if some patients received combination treatment with antibiotics	Success rates: OM of the long bones: 95 % FRI 60%

Vogt *et al.*, 2017	1	OM	Repeated dosing of phage cocktail Pyo bacteriophage through draining system, in combination with antibiotic therapy	Eradication of the infection
Ferry *et al.*, 2018a	1	OM (post-radiation)	Application of customised phage cocktail every 3 d, in combination with intravenous antibiotic therapy	Patient died 45 d after treatment due to cancer progression
Ferry *et al.*, 2018b	1	PJI	Single intraoperative injection of a customised phage cocktail in combination with intravenous antibiotic therapy	Eradication of the infection
Nir-Paz *et al.*, 2019	1	FRI	Intravenous repeated administration of customised phage cocktail, in combination with intravenous antibiotic therapy	Eradication of the infection (after two phage therapy regimens)
Tkhilaishvili *et al.*, 2019	1	PJI	Repeated dosing of customised phage cocktail, in combination with intravenous antibiotic therapy	Eradication of the infection
Onsea *et al.*, 2019	4	OM	Repeated dosing of BFC1 cocktail or Pyo bacteriophage cocktail in combination with intravenous antibiotic therapy	Eradication of the infection in all cases

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*



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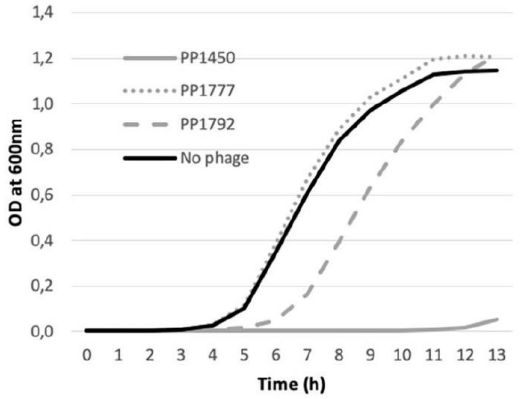

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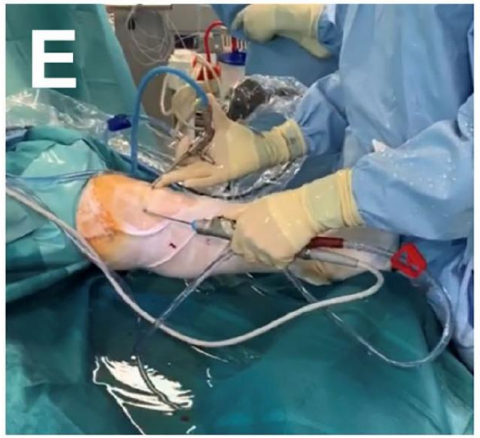
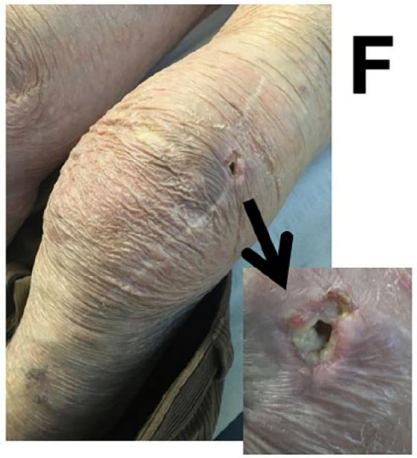
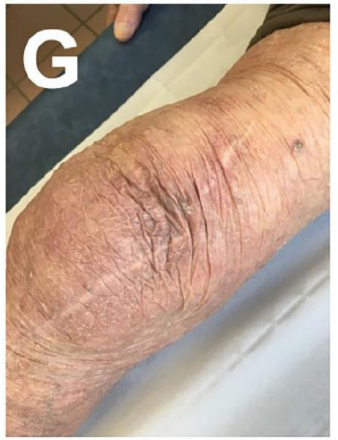
	PP1450	PP1777	PP1792
EOP	2.0×10^{-5}	4.0×10^{-6}	0
MCL (PFU/mL)	1.0×10^{7}	1.7×10^{8}	9.3×10^{8}







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

Edison J. Cano,[1,2] Katherine M. Caflisch,[2,3] Paul L. Bollyky,[4] Jonas D. Van Belleghem,[4] Robin Patel,[1,2,5] Joseph Fackler,[6] Michael J. Brownstein,[6] Bri'Anna Horne,[6] Biswajit Biswas,[7] Matthew Henry,[7,8] Francisco Malagon,[7] David G. Lewallen,[9] and Gina A. Suh[1]

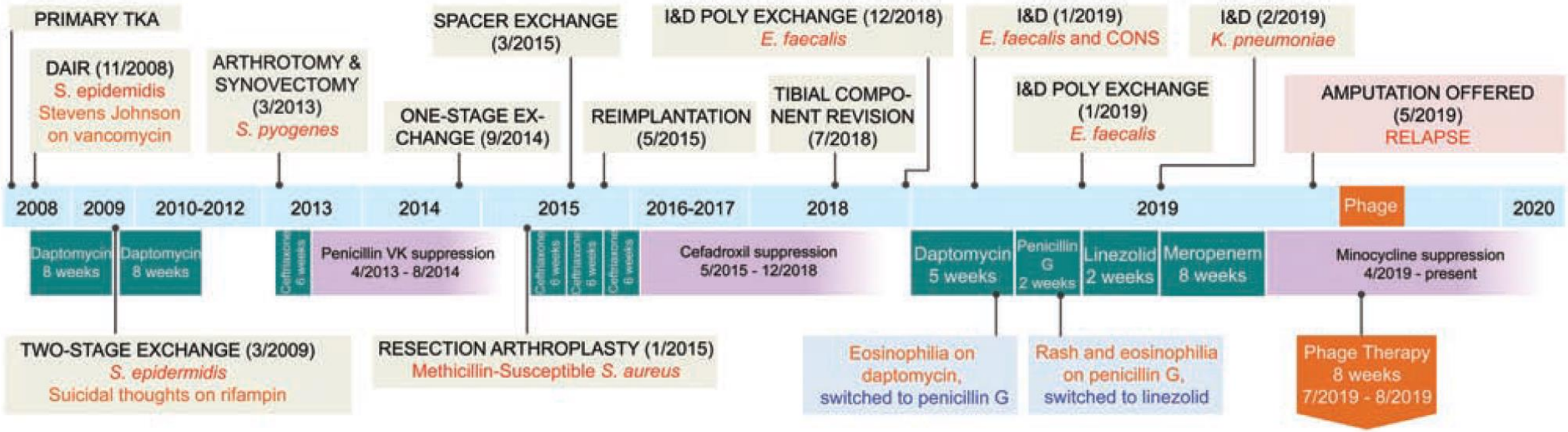


Figure 1. Summary of the patient's clinical course, timeline of surgical interventions, intraoperative cultures, antibiotics administered, and adverse events.

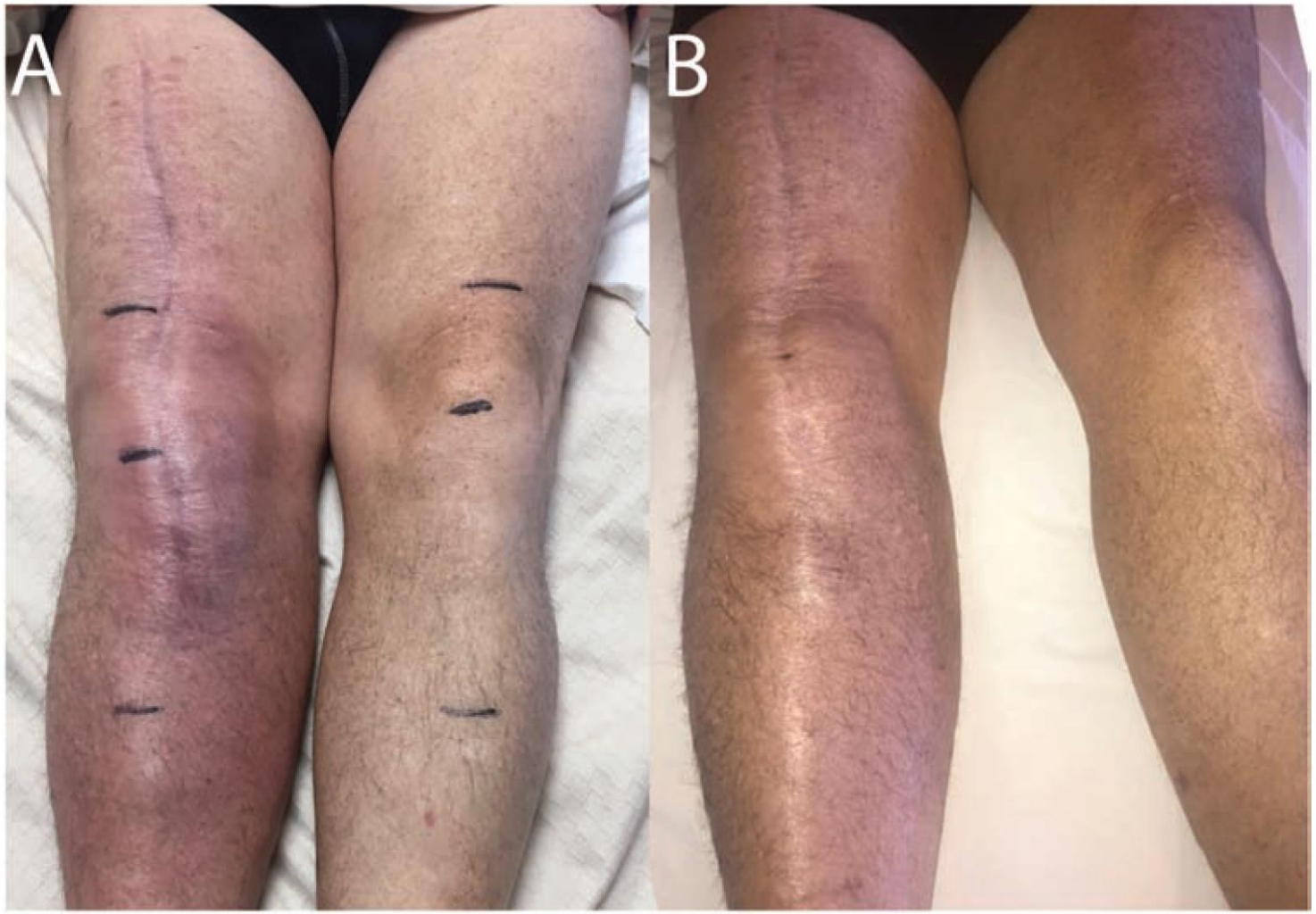


Figure 3. Phage therapy resulted in reduced erythema and swelling. Images are shown of the patient's lower extremities (*A*) before and (*B*) after completion of phage therapy.

Problematiche aperte

- Gestione dlle PJI in team muldisciplinari dedicati
- Definizione dell'infezione protesica, quando considerarla early o late
- Quali antibiotici scegliere in base all'attività sul biofilm, penetrazione ossea, sinergie, attività battericida, tollerabilità e sostenibilità
- Come stabilire un'infezione eradicata e decidere i timing del reimpianto e per quanto proseguire la terapia dopo reimpianto
- Prolungare il followup
- Organizzarsi per eventuale strategie alternative, come i batteriofagi