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BORDEAUX

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# NOUVEAUTÉS DANS L'ANTIBIOTHÉRAPIE DES INFECTIONS OSTÉO-ARTICULAIRES À BGN MULTI-RÉSISTANTS

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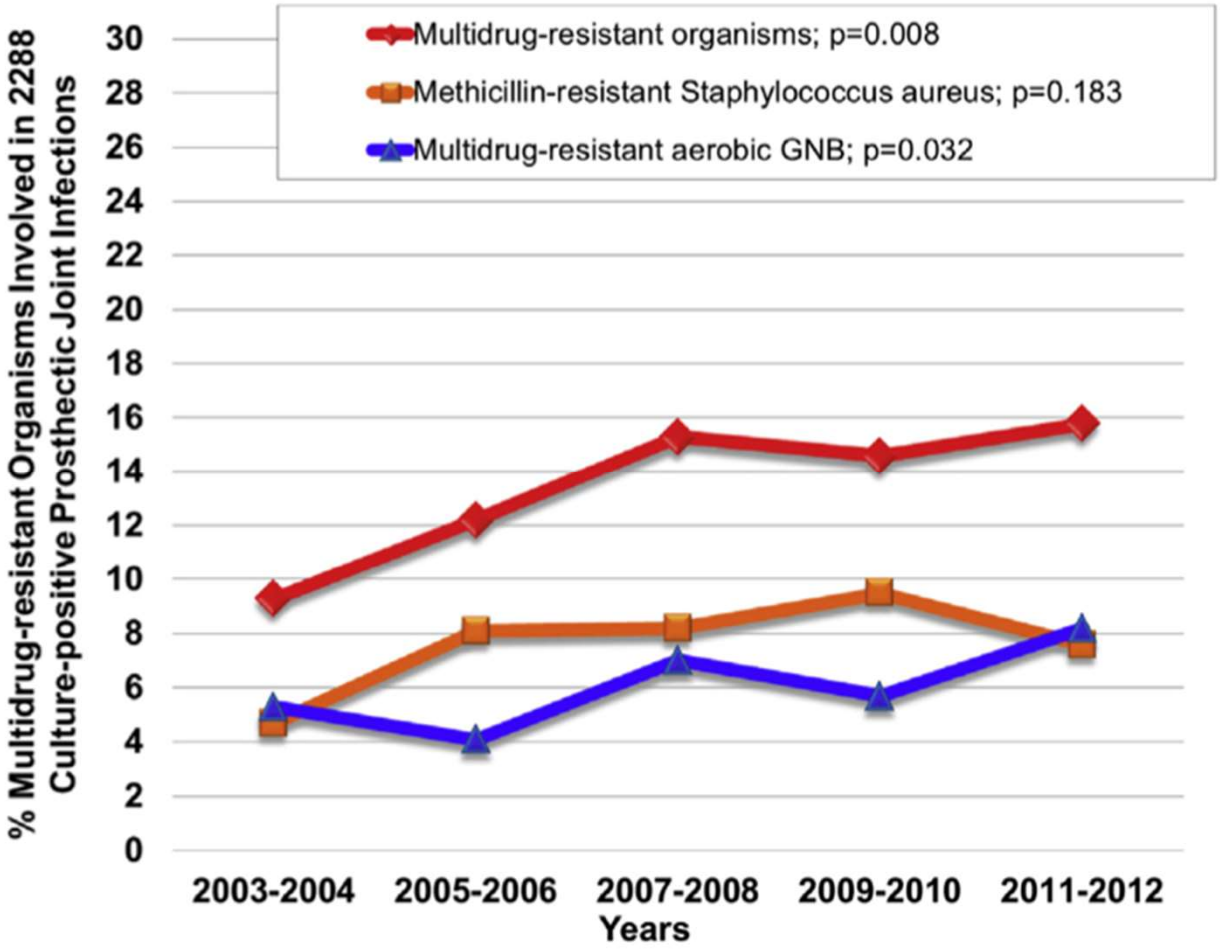
# Liens d'intérêt

- SANOFI, Pfizer, MSD, Eumedica, SHIONOGI, IBSA, GSK

# EPIDÉMIOLOGIE

# Time trends in the aetiology of prosthetic joint infections: a multicentre cohort study☆




Gram-negative bacteria (GNB) represent a significant cause of periprosthetic joint infection (PJI), accounting for approximately **25—30%** of early post-surgical and haematogenous cases

Benito N *et al.* CMI 2016

- We performed a cohort study in 19 hospitals in Spain, from 2003 to 2012. For each 2-year period (2003e2004 to 2011e2012), the incidence of microorganisms causing PJIs and multidrug-resistant bacteria was assessed. Temporal trends over the study period were evaluated.
- We included 2524 consecutive adult patients with a diagnosis of PJI. A microbiological diagnosis was obtained for 2288 cases (90.6%).
- Staphylococci were the most common cause of infection (1492, 65.2%).
- However, a statistically signi cant rising linear trend was observed for the proportion of infections caused by Gram-negative bacilli, mainly due to the increase in the last 2-year period (25% in 2003e2004, 33.3% in 2011e2012; p 0.024 for trend).
- No particular species contributed disproportionally to this overall increase. The percentage of multidrug-resistant bacteria PJIs increased from 9.3% in 2003e2004 to 15.8% in 2011e2012 (p 0.008), mainly because of the significant rise in multidrug-resistant Gram-negative bacilli (from 5.3% in 2003e2004 to 8.2% in 2011e2012; p 0.032). The observed trends have important implications for the management of PJIs and prophylaxis in
- joint replacements.

Epidemiology of healthcare-associated infections and mechanisms of antimicrobial resistance of responsible pathogens in Ukraine: a multicentre study

A. Salmanov [a] · D. Shchehlov [b] · O. Svyrydiuk [b] · I. Bortnik [b] · M. Mamonova [c] · S. Korniyenko [d] · V. Rud [e] · V. Artyomenko [d] · M. Gudym [b] · R. Maliarchuk [f] · T. Bondar [c]

37,968 patients, 6218 (16.4%) HAIs were observed

Surgical site infections (15.3%)

Antimicrobial **resistance to carbapenems** was detected in **71.3% of all non-fermentative Gram-negative bacteria**.

Of the all isolates tested, **25.1% were found to be multidrug-resistant (MDR).**

JHI 2023

› Antimicrob Agents Chemother. 2024 Nov 6;68(11):e0109024. doi: 10.1128/aac.01090-24. Epub 2024 Sep 20.

**Detection of cefiderocol and aztreonam/avibactam resistance in epidemic *Escherichia coli* ST-361 carrying $bla_{NDM-5}$ and $bla_{KPC-3}$ from foreign fighters evacuated from Ukraine**

Melissa J Martin [# 1], Ting L Luo [# 1], Valentyn Kovalchuk [2], Viacheslav Kondratiuk [3], Henry D Dao [1 4], Iryna Kovalenko [2], Brandon J Plaza [4], Joanna M Kettlewell [4], Cole P Anderson [4], Jason R Smedberg [4], Ana C Ong [1], Yoon I Kwak [1], Joshua S Hawley-Molloy [5], Jason W Bennett [1], Patrick T McGann [1], Francois Lebreton [1]

# JHI

- Methods
- Prospective multicentre surveillance was conducted from January 2019 to December 2021 in 17 regional hospitals of Ukraine. Definitions of HAIs were adapted from the Centers for Disease Control and Prevention's National Healthcare Safety Network.
- Findings
- Among 37,968 patients, 6218 (16.4%) HAIs were observed. Of all HAI cases, 14.8% were detected after hospital discharge. The most frequently reported HAI types were pneumonia (24.4%), urinary tract infections (19.8%), surgical site infections (15.3%), and bloodstream infections (11.2%). Of all HAIs, 11.9% were defined as part of an outbreak. Death during hospitalization was reported in 12.6% of HAI cases. In total, 85.1% isolates from patients were found to be MDROs. Meticillin resistance was found in 41.2% of *S. aureus* (MRSA) isolates, and vancomycin resistance was found in 11.8% of enterococci. Antimicrobial resistance to third-generation cephalosporins was detected in 48.4% of all Enterobacterales. Antimicrobial resistance to carbapenems was detected in 71.3% of all non-fermentative Gram-negative bacteria. Of the all isolates tested, 25.1% were found to be multidrug-resistant (MDR).
- Conclusion
- This study found a high prevalence of HAIs; those caused by MDROs varied widely depending on the bacterial species, antimicrobial group, and geographical region of Ukraine. MDROs were one of the main causes of HAI-associated deaths.

# CHIRURGIE

# Extended-Spectrum Beta-Lactamase Infections in Orthopedic-Related Devices and Prosthetic Joints

SURESH J. ANTONY, MD; MONISHA S. PARIKH, MD; ENRIQUE SOTO-RUIZ, PHARMD; CRAIG CAMERON, DO; RUPAL MODY, MD

Table

**Characteristics of Patients With ESBL Infections in Orthopedic-Related Devices and Prosthetic Joints**

| Case No./ Sex/Age, y | Comorbidities/Risk Factors | Clinical Presentation | Diagnostic Findings | Treatment and Course |
|---|---|---|---|---|
| 1/F/80 | Bilateral TKA<br>CAD, HTN, CVD with neurological deficits, chronic venous stasis, arthritis | Left leg wound infection/ open<br>Admission laboratory values: WBC, 26.07; CRP, 5.2; ESR, 55; +U/A | ESBL *Escherichia coli, Pseudomonas aeruginosa, Alcaligenes* species | Initial: ciprofloxacin and vancomycin<br>Changed to: only imipenem/ cilastatin 500 mg every 8 h IV started; D/C for 30 d |
| 2/F/74 | Right knee hardware repair, ORIF, s/p fracture 6 mo prior<br>HTN, cirrhosis | Bilateral sacral and hip wound infections/open<br>Admission laboratory values: WBC, 6.13; CRP, 0.81; ESR, 43; +U/A | ESBL *E coli, Klebsiella pneumoniae* | Initial: ceftriaxone 2 g every 24 h IV, levofloxacin 750 mg IVQD, metronidazole 500 mg every 8 h IV, vancomycin 1942.5 g every 12 h IV<br>Changed to: vancomycin 1 g every 12 h IV + piperacillin/tazobactam 4.5 g every 8 h IV<br>D/C on ertapenem 1 g every 24 h for 4 wk |
| 3/F/77 | MVA 1 mo prior with pelvis fracture with reduction, internal fixation, and iliosacral scews × 2<br>HTN, DM | Left hip wound infection/ closed<br>Admission laboratory values: WBC, 6.34; CRP, 9.69; ESR, 117; +U/A | ESBL *K pneumoniae, E coli, Bacteroides fragilis*<br>Surgical: multiple I&D | Initial: vancomycin 2 g × 1 IV + piperacillin/tazobactam 4.5 g × 1 IV<br>Changed to: ceftriaxone 1 g every 24 h IV × 10 d + imipenem/cilastatin 500 mg every 8 h IV for 14 d |
| 4/M/72 | DM, OA | Right TKA cellulitis<br>Admission laboratory values: WBC, 10.2; CRP, 10.2; ESR, 76 | ESBL *E coli*<br>Surgical: revision of TKA (2 stage) | IV ertapenem for 6 wk |
| 5/F/68 | HTN, OA | Right ORIF tibia nonhealing wound at operative site, open<br>Admission laboratory values: WBC, 12.4; CRP, 7.6; ESR, 46 | ESBL *E coli*<br>Surgical: I&D with hardware removal | IV ertapenem for 6 wk |
| 6/F/86 | OA, dementia | Right TKA infection<br>Admission laboratory values: WBC, 13.4; CRP, 0.4; ESR, 68 | ESBL *E coli*<br>Surgical: removal of TKA (2 stage) | Meropenem for 6 wk |

- Etude rétrospective de 6 cas avec IOA documentée sur per opératoire
- 3/6 polymicrobienne
- Comorbidités +++
- Bonne évolution si ablation matériel
- Traitement par carbapénèmes
- 6 semaines

Orthopaedics juil/aug 2016

# HSIEH CID 2009

- ***Methods.*** We performed a retrospective cohort analysis of all cases of PJI that were treated at our institution between 2000 and 2006.
- ***Results:*** GN microorganisms were involved in 53 (15.3%) of 346 first-time episodes of PJI, and Pseudomonas aeruginosa was the most commonly isolated pathogen (21 episodes; 40%). Patients with GN PJI were older (median age, 68 vs. 59 years, $p< 0.001$) and developed infection earlier (median joint age, 74 vs. 109 days, $p< 0.001$) than those with GP PJI. Fifty-one percent, 30%, and 19% of GN PJIs were treated with debridement, two-stage exchange, and resection arthroplasty, respectively. When compared to GP PJI, treating GN PJI with debridement was associated with a lower 2-year cumulative probability of success (27% vs. 47%, $p= 0.0016$); no difference was found when it was treated with two-stage exchange or resection arthroplasty. A longer duration of symptoms before debridement was associated with treatment failure for GN PJI (median, 11 vs. 5 days, $p= 0.02$).
- ***Conclusions:*** GN PJI represents a substantial proportion of all PJI occurrences. Debridement alone has a high failure rate and should not be attempted when the duration of symptoms is long. Resection of the prosthesis, with or without subsequent reimplantation for GN PJI is associated with a favorable outcome rate that is comparable to that associated with PJI due to GP pathogens.

## Gram-negative Prosthetic Joint Infections: Risk Factors and Outcome of Treatment

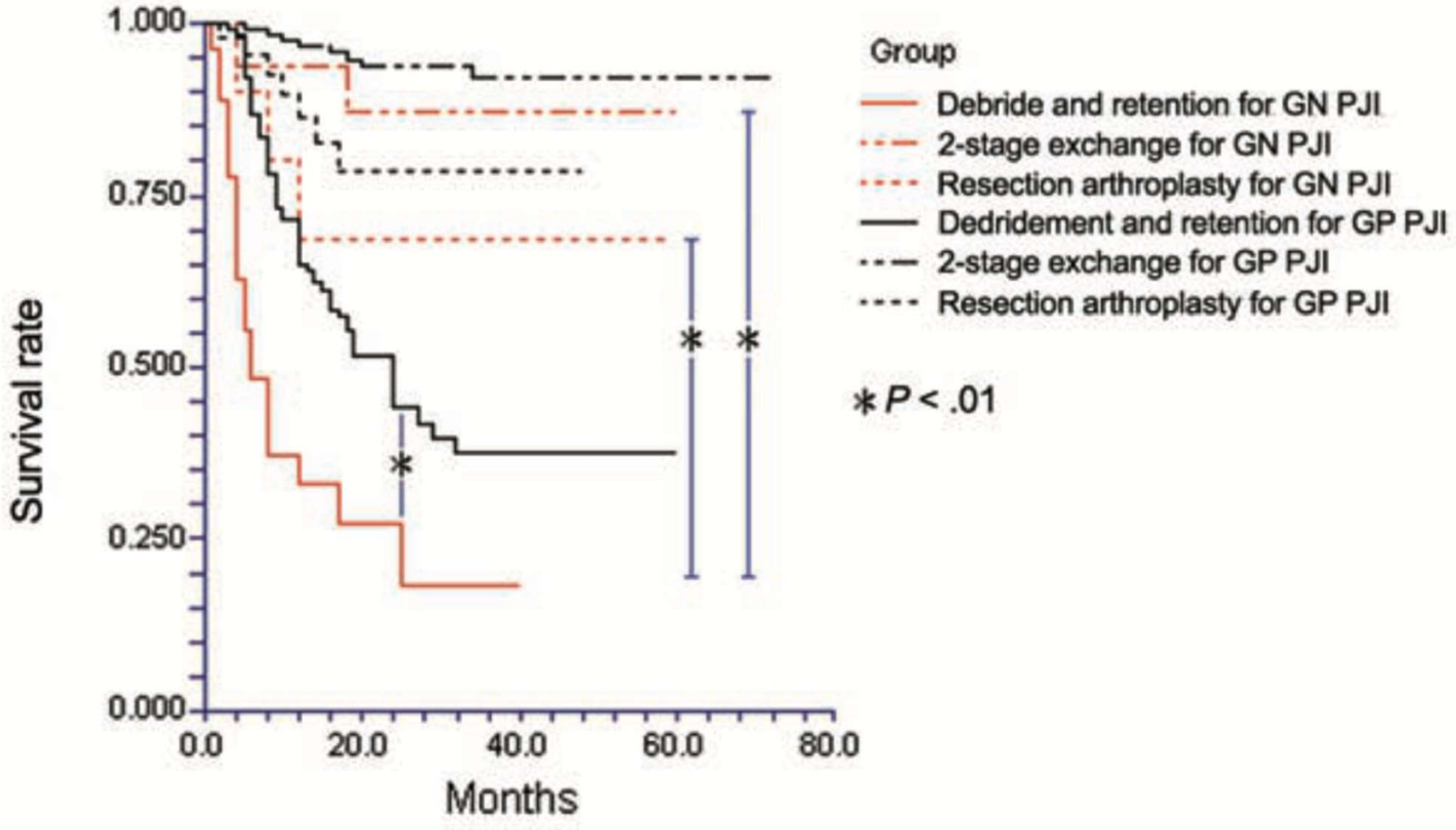
Get access

HSIEH CID 2009

| Caractéristique | PJI BGN (n=53) | PJI CGP (n=293) | p |
|---|---|---|---|
| Âge, médiane (années) [intervalle] | **68 (35–85)** | **59 (32–79)** | **<0,001** |
| Sexe masculin, (%) | 62 | 68 | 0,48 |
| Âge de la prothèse, médiane (jours) [intervalle] | 74 (8–296) | 109 (6–976) | <0,001 |
| Interventions multiples (≥2) avant PJI, (%) | 38 | 32 | 0,42 |
| Infection polymicrobienne, (%) | 4 | 5 | 0,75 |
| — Comorbidités — | | | |
| Diabète, n (%) | 40 | 37 | 0,67 |
| Polyarthrite rhumatoïde, (%) | 11 | 13 | 0,69 |
| Cancer, (%) | 6 | 4 | 0,71 |
| Cirrhose hépatique, (%) | 11 | 12 | 0,84 |
| Corticothérapie, (%) | 15 | 12 | 0,57 |
| — Présentation de l'infection — | | | |
| Fistule, (%) | 43 | 32 | 0,12 |
| Fièvre (température ≥38,3 °C), (%) | 19 | 11 | 0,09 |
| Bactériémie, (%) | 9 | 5 | 0,19 |
| — Type de chirurgie — | | | |
| DAIR, (%) | 51 | 43 | 0,31 |
| Changement 2 temps, (%) | 30 | 40 | 0,17 |
| Résection arthroplastie, (%) | 19 | 16 | 0,66 |

## Gram-negative Prosthetic Joint Infections: Risk Factors and Outcome of Treatment

Get access



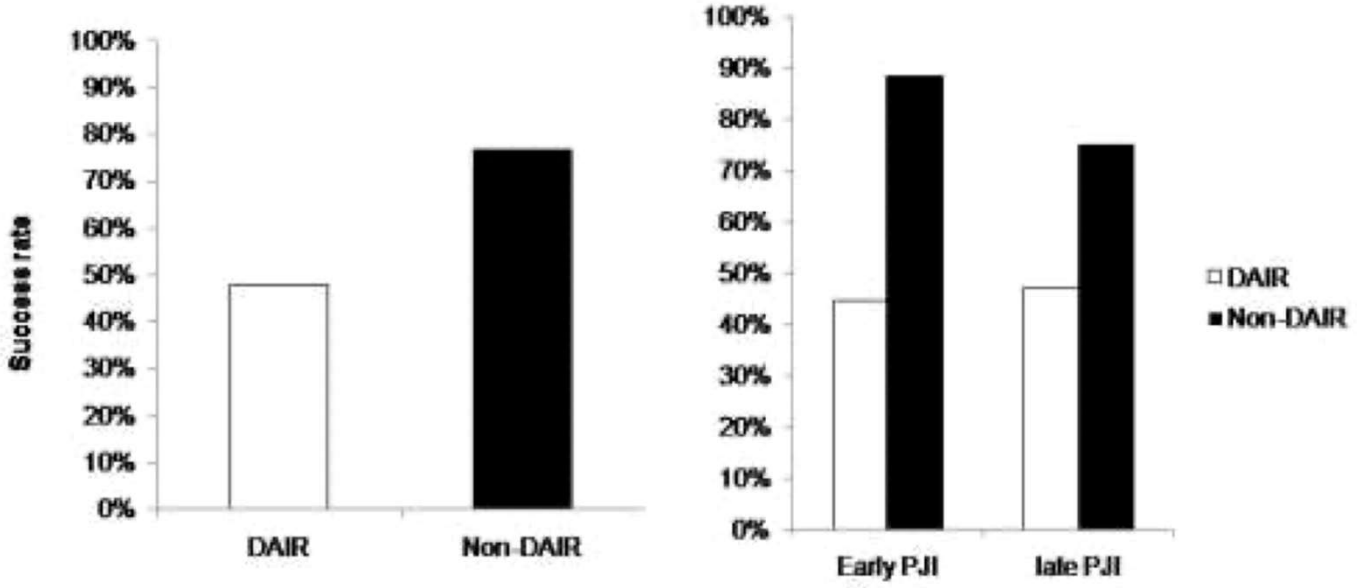

HSIEH CID 2009

# Multidrug-resistant and extensively drug-resistant Gram-negative prosthetic joint infections: Role of surgery and impact of colistin administration

| Variables | DAIR (N=67; 51,1%) | Non-DAIR (N=64; 48,9%) | Total (N=131) | p-value* |
|---|---|---|---|---|
| Âge (ans), moyenne ± écart-type | 74,6 ± 11,4 | 71,4 ± 13,9 | 73,0 ± 12,7 | 0,149 |
| Sexe (Homme), (%) | 31,3 | 40,6 | 35,9 | 0,281 |
| Comorbidités (%) | 56,7 | 60,9 | 58,8 | 0,723 |
| Diabète (%) | 26,9 | 37,5 | 32,1 | 0,261 |
| Polyarthrite rhumatoïde (%) | 13,4 | 7,8 | 10,7 | 0,399 |
| Cancer (%) | 6,0 | 9,4 | 7,6 | 0,525 |
| Insuffisance rénale chronique (%) | 13,4 | 9,4 | 11,5 | 0,586 |
| Bacilles Gram négatifs (XDR) (%) | 19,4 | 15,6 | 17,6 | 0,649 |
| Administration de colistine (%) | 22,4 | 21,0 | 21,7 | 1,000 |
| Monothérapie/Polythérapie, n (%) | 25,4 | 38,7 | 31,8 | 0,131 |
| Durée totale des antibiotiques (jours), moyenne ± ET | 77,7 ± 63,4 | 70,1 ± 72,9 | 74,3 ± 67,6 | 0,545 |
| infection Précoce (%) | 73,4 | 48,1 | 61,9 | **0,007** |
| Succès, (%) | 47,8 | 76,6 | 61,8 | **0,001** |

Papadoulos *et al.* IJAA 2019

# Multidrug-resistant and extensively drug-resistant Gram-negative prosthetic joint infections: Role of surgery and impact of colistin administration




Papadoulos *et al.* IJAA 2019

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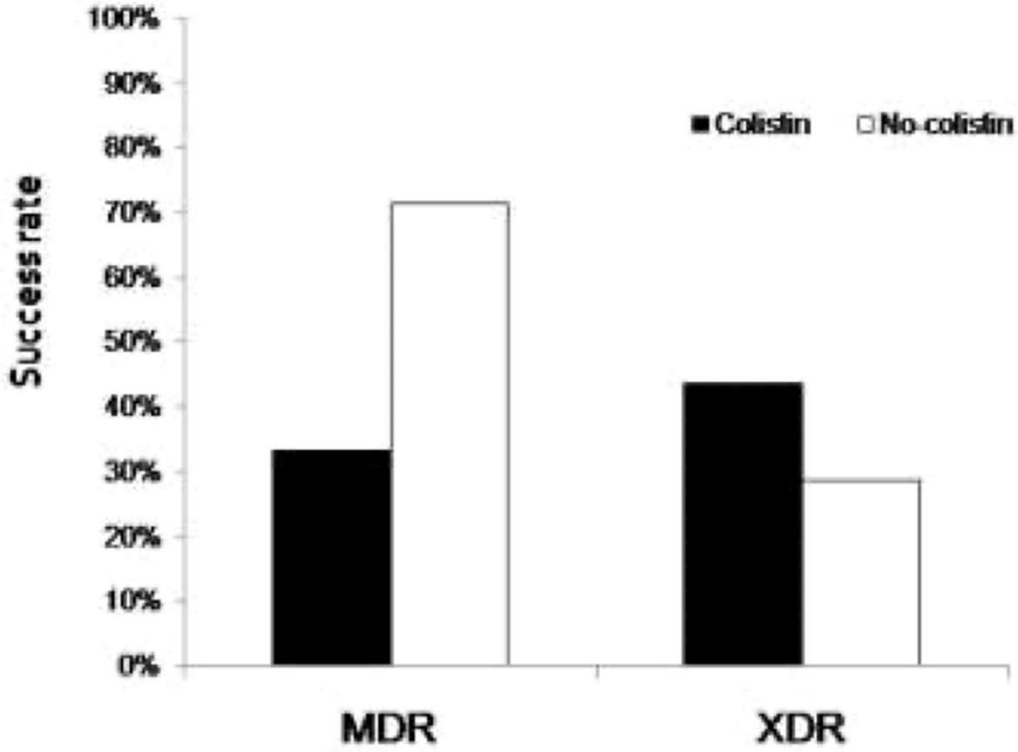



Papadoulos *et al.* IJAA 2019

# IJAA 2019

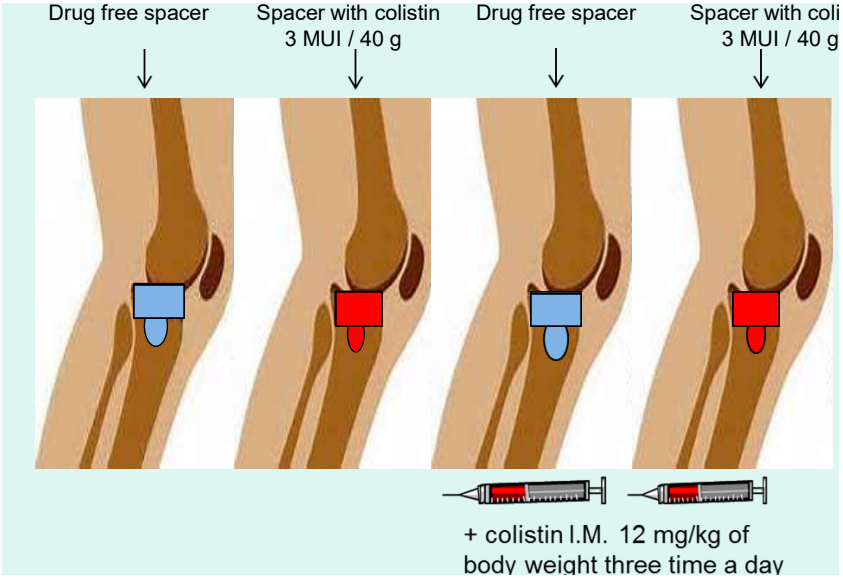
- Factors influencing treatment outcome of patients with Gram-negative bacterial (GNB) multidrug-resistant (MDR) and extensively drug-resistant (XDR) prosthetic joint infection (PJIs) were analysed.
- Data were collected (2000-2015) by 18 centres. Treatment success was analysed by surgery type for PJI, resistance (MDR/XDR) and antimicrobials (colistin/non-colistin) using logistic regression and survival analyses.
- A total of 131 patients (mean age 73.0 years, 35.9% male, 58.8% with co-morbidities) with MDR (n = 108) or XDR (n = 23) GNB PJI were assessed. The most common pathogens were Escherichia coli (33.6%), Pseudomonas aeruginosa (25.2%), Klebsiella pneumoniae (21.4%) and Enterobacter cloacae (17.6%).
- Pseudomonas aeruginosa predominated in XDR cases. Isolates were carbapenem-resistant (n = 12), fluoroquinolone-resistant (n = 63) and ESBL-producers (n = 94). Treatment outcome was worse in XDR versus MDR cases (P = 0.018). Success rates did not differ for colistin versus non-colistin in XDR cases (P = 0.657), but colistin was less successful in MDR cases (P = 0.018).
- Debridement, antibiotics and implant retention (DAIR) (n = 67) was associated with higher failure rates versus non-DAIR (n = 64) (OR = 3.57, 95% CI 1.68-7.58; P < 0.001). Superiority of non-DAIR was confirmed by Kaplan-Meir analysis (HR = 0.36, 95% CI 0.20-0.67) and remained unchangeable by time of infection (early/late), antimicrobial resistance (MDR/XDR) and antimicrobials (colistin/non-colistin) (Breslow-Day, P = 0.737). DAIR is associated with higher failure rates even in early MDR/XDR GNB PJIs versus implant removal.
- Colistin should be preserved for XDR cases as it is detrimental in MDR infections.

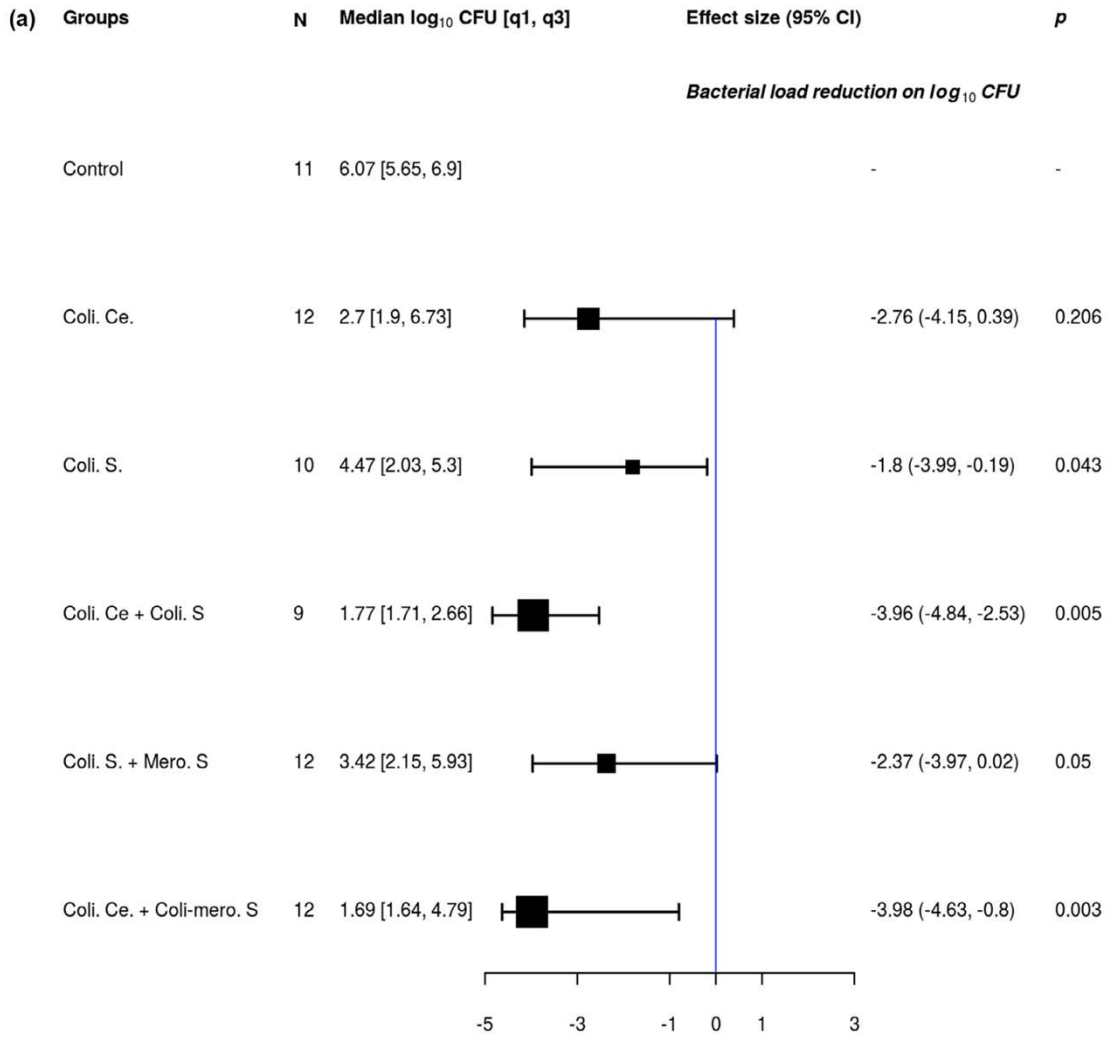
# Population type/FDR d'échec

# ANTIBIOTHÉRAPIE LOCALE

Colistin-containing cement spacer for treatment of experimental carbapenemase-producing *Klebsiella pneumoniae* prosthetic joint infection ☆

L. Gatin[a,b], A. Saleh Mghir[a], W. Mouton[c], F. Laurent[c], I. Ghout[d], N. Rioux-Leclercq[e], P. Tattevin[f,1,*], M.C. Verdier[g,1], A.C. Cremieux[a,h]




IJAA 2019

# The stability of carbapenems before and after admixture to PMMA-cement used for replacement surgery caused by Gram-negative bacteria

Matthias Schmid[1,2], Oliver Steiner[2], Lisa Fasshold[2], Walter Goessler[2], Anna-Maria Holl[3] and Klaus-Dieter Kühn[1*]

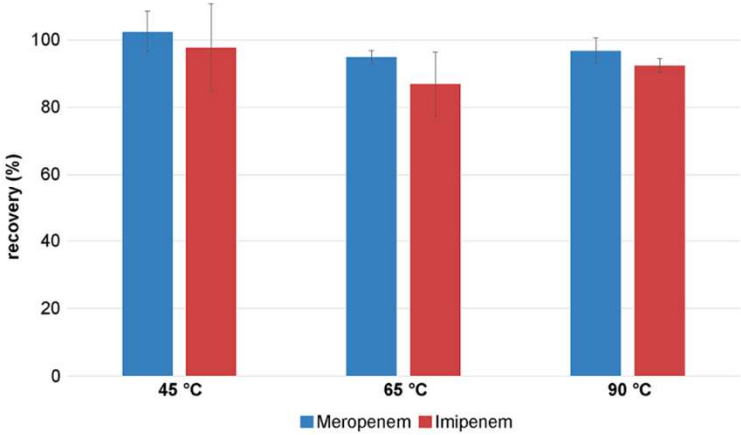



**Fig. 7** Recovery of temperature stressed meropenem and imipenem in powder after 120 min ($n = 5$)

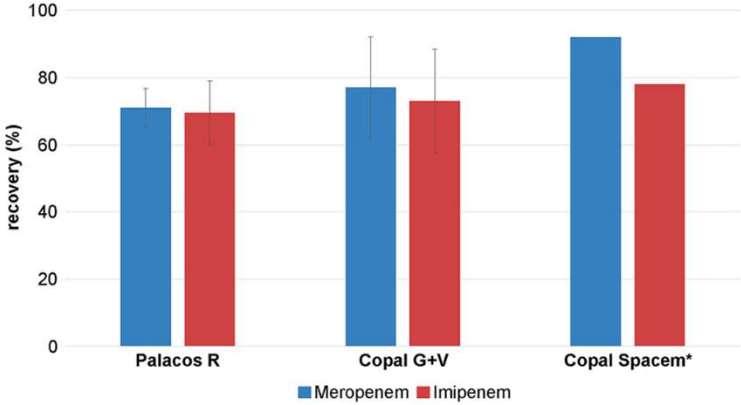



**Fig. 8** Recovery of 250 mg meropenem or imipenem after polymerization in three different PMMA bone cements. Palacos® R: $n = 4$; Copal® G + V: $n = 3$; Copal® spacem: $n = 1$. * There is no standard deviation at Copal® spacem because tests were performed only once

- Carbapenemase-producing Enterobacteriaceae (CPE) are emerging multidrug-resistant bacteria responsible for invasive infections, including prosthetic joint infections (PJIs). Local administration of colistin may provide bactericidal concentrations in situ. This study evaluated the efficacy of a colistin-impregnated cement spacer, alone and in combination with systemic antibiotics, in a rabbit model of CPE-PJI.
- Elution of 3 MIU of colistimethate sodium (CMS) in 40 g of poly(methyl methacrylate) cement was studied in vitro. In vivo, 5× 108 CFU of KPC-producing Klebsiella pneumoniae (colistin and meropenem MICs of 1 mg/L and 4 mg/L, respectively) were injected close to a prosthetic knee.
- Surgical debridement and prosthesis removal were performed 7 days later, and rabbits were assigned to six treatment groups (11–13 rabbits each): drug-free spacer; colistin-loaded spacer; colistin intramuscular (i.m.); colistin i.m.+ colistin spacer; colistin i.m.+ meropenem subcutaneous (s.c.); and colistin i.m.+ meropenem s.c.+ colistin spacer.
- Systemic treatment was administered at doses targeting pharmacokinetics in humans, and rabbits were euthanised 7 days later to evaluate bacterial counts in infected bones. In vitro, CMS elution was low (<0.1% at 24 h) but reached a local concentration of ≥20 mg/L (>20× MIC).
- In vivo, combinations of local and systemic colistin, with or without meropenem, were the only regimens superior to the control group ($P \leq 0.05$) in terms of viable bacterial counts and the proportion of rabbits with sterile bone, with no emergenceof colistin-resistant strains. Colistin-loaded cement spacer in combination with systemic antibiotics were the most effective regimens in this CPE-PJI model.

# Stratégie ATB : nouvelles molécules

- Modèles expérimentaux
- Quelles molécules pour quels germes
- E BLSE : carbasparring
- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.

# NOUVEAUX ANTIBIOTIQUES

| Antibiotique | Mécanisme d'action | Spectre d'activité (BGN MDR) | Limitations |
|---|---|---|---|
| **Carbapénèmes (p.ex. méropénem, imipénem–cilastatine, ertapénem)** | Inhibent la synthèse de la paroi en se liant aux PBP | ESBL | Aucune activité sur les carbapénémases, DTR A. baumannii, DTR P. aeruginosa ; l'ertapénem est inactif sur P. aeruginosa |
| **Méropénem–vaborbactam** | Méropénem : inhibe la synthèse de la paroi ; vaborbactam : inhibe les β-lactamases KPC | ESBL ; KPC | Pas d'activité sur les MBL ou carbapénémases de type OXA ; DTR P. aeruginosa ; DTR A. baumannii |
| **Imipénem–cilastatine–relebactam** | Imipénem : inhibe la synthèse de la paroi ; relebactam : inhibe KPC | ESBL ; KPC ; DTR P. aeruginosa ; (relebactam peut légèrement potentialiser l'activité d'imipénem contre certaines carbapénémases OXA) | Aucune activité sur les MBL |
| **Ceftolozane–tazobactam** | Ceftolozane : inhibe la synthèse de la paroi ; tazobactam : inhibe des β-lactamases | ESBL ; DTR P. aeruginosa | Pas d'activité sur les carbapénémases ; DTR A. baumannii ; β-lactamases AmpC |
| **Ceftazidime–avibactam** | Ceftazidime : inhibe la synthèse de la paroi ; avibactam : inhibe des β-lactamases dont KPC et OXA-48 | ESBL ; KPC ; β-lactamases AmpC ; carbapénémase OXA-48 ; DTR P. aeruginosa | Aucune activité sur les MBL ; taux de résistance élevés chez A. baumannii |
| **Cefidérocol** | Céphalosporine sidérophore : transport actif via systèmes d'uptake du fer | ESBL ; KPC ; MBL ; β-lactamases AmpC ; carbapénémase OXA-48 ; DTR P. aeruginosa ; DTR A. baumannii | — |
| **Fosfomycine** | Inhibe la synthèse de la paroi (cible MurA) | ESBL ; CRE (toutes classes de carbapénémases, y c. MBL) ; DTR P. aeruginosa | La monothérapie est généralement déconseillée |
| **Colistine** | Désorganise la membrane externe en se liant au LPS et aux phospholipides | ESBL ; CRE (toutes classes de carbapénémases, y c. MBL) ; DTR P. aeruginosa ; DTR A. baumannii | À utiliser en association avec ≥1 agent supplémentaire actif (CMI sensible) |
| **Tigécycline** | Inhibe la synthèse protéique (liaison à la sous-unité 30S) | ESBL ; CRE (toutes classes de carbapénémases, y c. MBL) ; DTR A. baumannii | Inactif contre P. aeruginosa |

Challenges and strategies in the treatment of periprosthetic joint infection caused by multidrug-resistant Gram-negative bacteria: a narrative review

Gomez-Junyent et al. CMI 2025

| Type de micro-organisme | Traitement antimicrobien |
|---|---|
| **BGN sensibles aux fluoroquinolones** | Fluoroquinolones |
| **BGN résistants aux fluoroquinolones** | β-lactamines i.v. |
| **Enterobacterales — TMP/SMX sensibles** | β-lactamines + colistine OU TMP/SMX[1r] |
| **Enterobacterales — TMP/SMX résistants** | β-lactamines + colistine[1h] |
| **Enterobacterales — schéma à base de β-lactamine** | |
| **• Hyper-production d'AmpC** | Méropénem OU Ertapénem OU Céfépime |
| **• BLSE** | Méropénem OU Ertapénem |
| **• Carbapénémase KPC** | Ceftazidime–avibactam OU Méropénem–vaborbactam OU Imipénem–relebactam |
| **• Carbapénémase OXA-48** | Ceftazidime–avibactam OU Céfépime–enmetazobactam |
| **• Métallo-β-lactamase (MBL)** | Cefidérocol OU Aztréonam–avibactam |
| ***Pseudomonas aeruginosa* — schéma à base de β-lactamine** | β-lactamines + colistine[1j] |
| ***P. aeruginosa* — souche sensible aux carbapénèmes[1j]** | Méropénem |
| ***P. aeruginosa* — DTR (sans MBL)** | Ceftolozane–tazobactam OU Ceftazidime–avibactam[1i] |
| ***P. aeruginosa* — DTR (avec MBL)** | Cefidérocol OU Aztréonam–avibactam |

**Efficacy and safety of colistin plus beta-lactams for bone and joint infection caused by fluoroquinolone-resistant gram-negative bacilli: a prospective multicenter study**

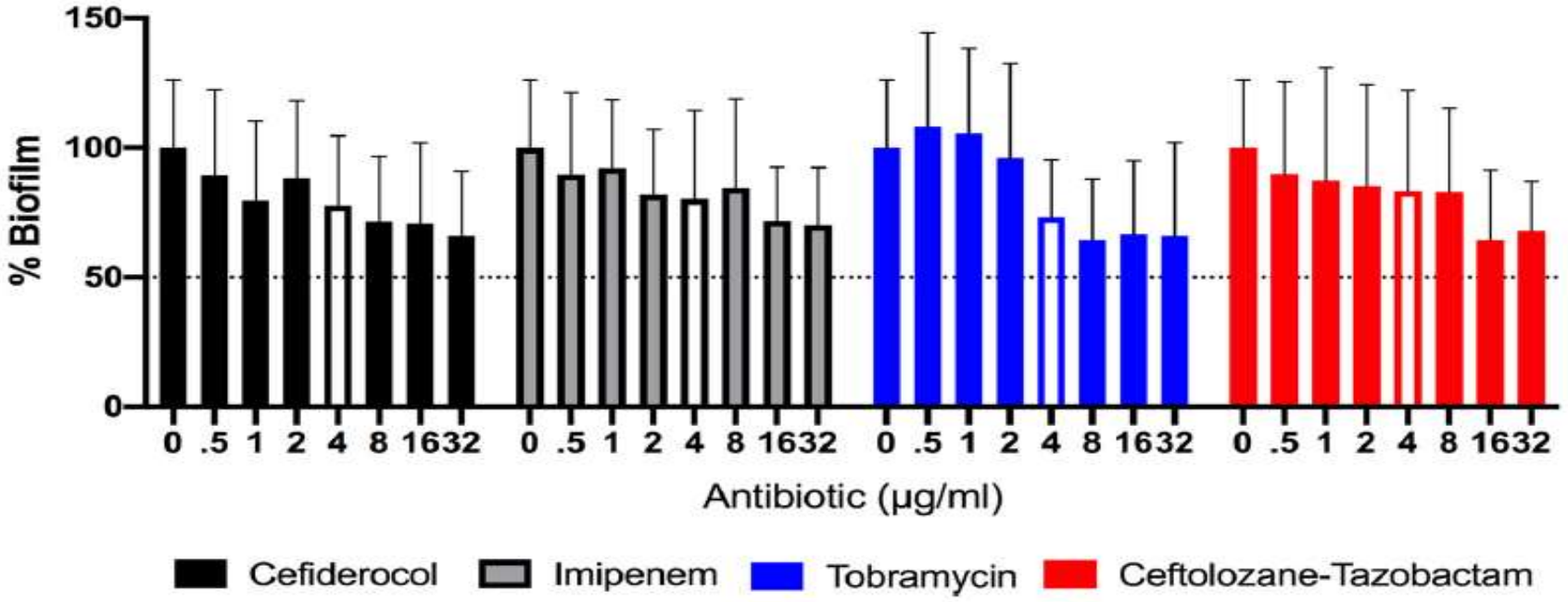
- Étude **observationnelle, prospective, non comparative, multicentrique**
- **IOA à BGN FQ R**
- **Chirurgie** + **β-lactamines IV + colistine ≥21 jours**.
- **44** cas ; âge médian **72 ans** (IQR 50–81) ; **32 (73 %)** infections liées à un **dispositif orthopédique**, dont **17 (39 %)** prothèses.
- **Enterobacterales** : **27 (61 %)** épisodes.
- **Pseudomonas spp.** : **17 (39 %)** épisodes.
- **BGN MDR/XDR** : **27/44 (61 %)**.
- **Traitement**
- **Colistine + β-lactamine IV** pendant **28 jours** (IQR 22–37), puis **β-lactamine IV seule** pendant **19 jours** (IQR 5–35).
- **Guérison globale : 82 %** (IC95 % 68–90).
- **Guérison avec rétention d'implant : 80 %** (IC95 % 55–93).
- **Tolérance**
- **Événements indésirables (EI) entraînant l'arrêt** des antimicrobiens : **10 (23 %)**, **tous réversibles**.

| Variables | Analyse univariée — OR (IC95 %) | p | Analyse multivariée — aOR (IC95 %) | p |
|---|---|---|---|---|
| Âge (par année) | 1,06 (1,01–1,12) | 0,032 | 1,13 (0,96–1,33) | 0,145 |
| Indice de comorbidités de Charlson (par unité) | 1,63 (0,97–2,76) | 0,068 | — | — |
| Concentration médiane de colistine (par mg/L) | 7,47 (2,12–26,3) | 0,002 | 4,74 (1,23–18,2) | 0,023 |
| Dose de CMS ≥ 9 MU/jour | 0,52 (0,14–2,01) | 0,347 | — | — |
| Créatinine de base (par mg/dL) | 1,85 (0,15–23,1) | 0,632 | — | — |

Mancheño-Losa Infection 2025

# Cefiderocol Retains Antibiofilm Activity in Multidrug-Resistant Gram-Negative Pathogens

Christine A. Pybus,[a] Christina Felder-Scott,[b] Victor Obuekwe,[a] David E. Greenberg[a,c]




AAC 2021

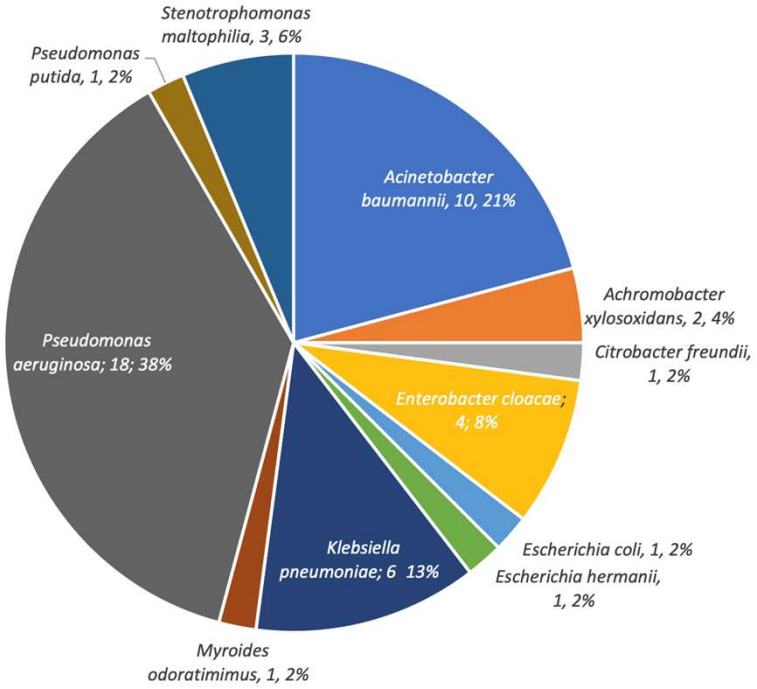
antibiotics

MDPI

Article

# Real-Life Cefiderocol Use in Bone and Joint Infection: A French National Cohort

Ava Diarra [1,2,*], Maxime Degrendel [3], Isabelle Eberl [4], Tristan Ferry [5,6], Karim Jaffal [7], Lelia Escaut [8], Antoine Asquier-Khati [9], Nicolas Taar [10], Johan Courjon [11,12], Laurène Deconinck [13], Benjamin Lefevre [14,15], Aurélie Baldolli [16], Messaline Bermejo [17], Alexandre Bleibtreu [18], Vincent Dacquet [19], Victoire de Lastours [20], Pierre Gazeau [21], Romaric Larcher [22], Pierre Patoz [23], Olivier Robineau [1,24,25], Nicolas Rouzic [26], Naomi Sayre [27], Diana Isabela Costescu Strachinaru [28], Benjamin Valentin [29], Heidi Wille [30] and Eric Senneville [1]




22 centres français,
45 patients inclus.
73 % d'hommes ;
Age médian : 62 ans (IQR 29) ;
Score de Charlson médian = 3.
Type d'infection : PJI dans 20 cas (44 %).
Microbiologie : BGN producteurs de carbapénémase 74 % des cas (17/23), dont *Pseudomonas aeruginosa* 38 %
Cefiderocol : 6 g/j en association dans 40/45 cas (89 %).
Durée de traitement : médiane 34 jours.
Tolérance : 7 patients (16 %) ont eu des effets indésirables,.
Evolution : échecs 22/45 (49 %) ; décès 10/45 (22 %).

Antibiotics 2025

# Revue de la littérature

| Etude | N patients | Types d'infection | Bactéries | Evolution |
|---|---|---|---|---|
| Dagher *et al.* | 1 | Ostéomyélite | *A. baumannii* XDR (OXA-23)<br>*Enterococcus faecalis*<br>*Corynebacterium striatum* | Favorable |
| Bleibtreu *et al.* | 2 | Infection ostéoarticulaire n=1<br>Infection sur prothèse n=1 | *Enterobacter hormaechei* subsp. *Hoffmannii* XDR<br>*K. pneumoniae* (OXA-48) | Favorable 1/2 |
| Oliva *et al.* | 1 | SDI n=1 | *P. aeruginosa* XDR | Favorable |
| Zingg *et al.* | 2 | Ostéomyélite n=1<br>Infection de matériel spinal n=1 | *A. baumannii* (souches OXA-23, OXA-40 + NDM, OXA-23 + OXA-58) | Favorable 2/2 |
| Alamarat *et al.* | 1 | Ostéomyélite | *P. aeruginosa* (NDM)<br>*K. pneumoniae* (BLSE) | Favorable |
| Simeon *et al.* | 1 | Infection sur prothèse ostéoarticulaire | *Enterobacter hormaechei* subsp. *Hoffmannii* XDR | Favorable |
| Mabayoje *et al.* | 1 | Infection sur prothèse ostéoarticulaire | *A. baumannii* XDR | Favorable |
| Cipko *et al.* | 1 | Infection de matériel spinal | *A. baumannii* XDR<br>*P. aeruginosa* | Favorable |
| *Chavda et al.* | 1 | IOA | *Pseudomonas aeruginosa* IMP,<br>Morganella Morganii | Favorable |
| *Mabayoje et al* | 1 | IOA | *Acinetobacter baumanii* NDM | Favorable |
| *Carney et* | 1 | IOA | *E. coli* NDM | Favorable |

Expert Review of Anti-infective Therapy

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**Intravenous fosfomycin for the treatment of patients with bone and joint infections: a review**

Katerina G. Tsegka, Georgios L. Voulgaris, Margarita Kyriakidou, Anastasios Kapaskelis & Matthew E. Falagas

| Références | N patient | Âge | Indication | Pathogènes | ATB associés | Dose | Posologie | Durée | Evolution | EI |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baron et al., France, 2019** | 1 | 43 ans | Pseudoarthrose septique | Klebsiella pneumoniae productrice de carbapénémase | Colistine IV, doxyxycline PO | 12 g | 4 g q8 h | 3 mois | Guérison | Aucun |
| **Narayanasamy et al., Australie, 2020** | 1 | 75 ans | Infection sur matériel d'ostéosynthèse | Pseudomonas aeruginosa XDR producteur de carbapénémase | Colistine | 3 g PO 3 jours puis 16 g IV | 4 g q6 h | 82 jours | Guérison | Atteinte rénale liée à la colistine |

## Real-World Use, Effectiveness, and Safety of Intravenous Fosfomycin: The FORTRESS Study

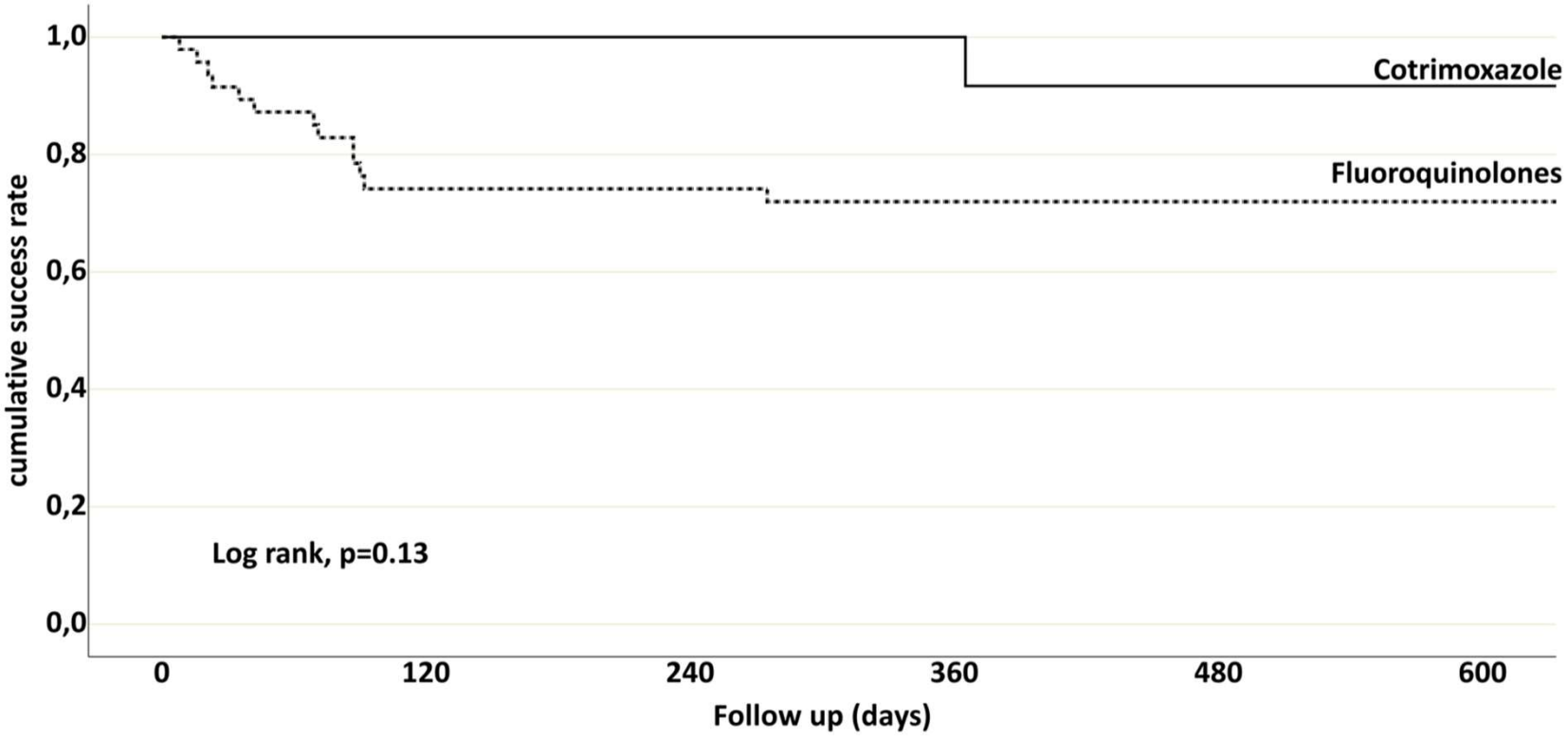
| Sous-groupes | N Cas | Succès clinique, (%) | Guérison microbiologique (%) |
|---|---|---|---|
| Tous les patients | 716 | 75,3 | 82,4 |
| Infections ostéo-articulaires | 124 | 72,6 | 81,5 |
| Dose quotidienne > 16 g/d | 18 | 83,3 | 83,3 |
| Dose quotidienne ≤ 16 g/d | 106 | 70,8 | 81,1 |
| — Détails BJI — | | | |
| Spondylodiscite | 53 | 62,3 | 69,8 |
| PJI | 25 | 84,0 | 92,0 |
| Ostéomyélite os long | 10 | 70,0 | 80,0 |
| Pied diabétique — ostéomyélite | 7 | 57,1 | 71,4 |
| Autres ostéomyélites | 29 | 86,2 | 96,6 |

Bodmann et al. Infect Dis Ther (2025)

# Bactrim


- Hanssen JLJ, van der Wal RJP, Mahdad R, Keizer S, Delfos NM, van der Lugt JCT, et al. Targeted antimicrobial regimens for Gram-negative prosthetic joint infections: A prospective multicenter study. Antimicrob Agents Chemother 2024;68:e0123224. https://doi.org/10.1128/aac.01232—24.
- [36] Lecomte R, Deschanvres C, Le Bourgeois A, Bart G, Mahieu R, Le Moal G, et al. Efficacy and safety of co-trimoxazole in device-related bone and joint infections: A CRIOGO multicentre case-control study. J Antimicrob Chemother 2024;79:3109—15. https://doi.org/10.1093/jac/dkae328.

## Targeted antimicrobial regimens for Gram-negative prosthetic joint infections: a prospective multicenter study




Hanssen AAC 2024

# Hanssen

- We aimed to compare different targeted antimicrobial strategies for GN-PJI managed by debridement, antibiotics, and implant retention (DAIR) or one-stage revision surgery (1SR) and to review the literature of oral treatment options for GN-PJI.
- In this prospective, multicenter, registry-based study, all consecutive patients with a PJI caused by a Gram-negative microorganism (including mixed infections with Gram-positive microorganisms), managed with DAIR or 1S from 2015 to 2020, were included. Minimum follow-up was 1 year. Patients underwent targeted therapy with oral FQ, oral cotrimoxazole, or intravenous or oral β-lactams.
- Survival analysis was performed with use of Kaplan-Meier and Cox proportional hazards models to identify factors potentially associated with treatment failure.
- Seventy-four patients who received either FQ (n = 47, 64%), cotrimoxazole (n = 13, 18%), or β-lactams (n = 14, 18%) were included. Surgical strategy consisted of DAIR (n = 72) or 1SR (n = 2).
- Median follow-up was 449 days (interquartile range 89–738 days). Failure free survival did not differ between the FQ (72%) and cotrimoxazole (92%) groups (log rank, P = 0.13).
- This outcome did not change when excluding all pseudomonal PJI in the FQ group. Cotrimoxazole is a potential effective targeted antimicrobial therapy for patients with GN-PJI. A randomized controlled trial is needed to confirm the findings of this study.

# R Lecomte

- Methods: This multicentre case–control study included consecutive adult patients diagnosed with device-related BJI. Each patient receiving co-trimoxazole was included in the co-trimoxazole group and was matched with two control patients, with stratification on microbial aetiology and age. The primary outcome was composite and defined by death or treatment failure during the follow-up.
- Results: In this study, 150 patients were included, 50 in the co-trimoxazole group and 100 in the control group.
- The rate of reaching the primary endpoint was 18% in the co-trimoxazole group (9/50 cases) versus 21% in the control group (21/100) (P = 0.66). Co-trimoxazole use was not associated with an unfavourable outcome in the multivariate analysis (adjusted OR 0.8, 95% CI 0.31–2.06, P = 0.64). Although no significant difference was observed in premature discontinuation of treatment due to an adverse event between both groups (14 versus12%, P = 0.73), treatment-related adverse events were significantly more frequently reported in patients of the co-trimoxazole group than the control group [34% (17/50) versus 18% (18/100), P = 0.03].
- Conclusions: Co-trimoxazole appears to be an effective alternative for the treatment of BJI, even when it occurs on a device, but the safety profile requires close monitoring of adverse effects.

**Efficacy and safety of co-trimoxazole in device-related bone and joint infections: a CRIOGO multicentre case–control study**

Raphaël Lecomte[1,2]*, Colin Deschanvres [1,2], Amandine Le Bourgeois[3], Géraldine Bart[4], Rafaël Mahieu[5], Gwénaël Le Moal[6], Séverine Ansart[7], Nathalie Asseray[1,2], Louise Ruffier d'Epenoux[8], Stéphane Corvec [8,9] and David Boutoille [1,2]; on behalf of the CRIOGO network†

| Variables | Groupe co-trimoxazole (N=50) | Groupe contrôle (N=100) | p-valeur |
|---|---|---|---|
| Âge, années, médiane (IQR) | 64 (48–83) | 65 (49–76) | 0,39 |
| Sexe masculin, n (%) | 60 | 62 | 0,81 |
| — Comorbidités — | | | |
| Indice de Charlson, médiane (IQR) | 3 (1–5) | 2,5 (1–4) | 0,62 |
| Insuffisance rénale chronique, n (%) | 6 | 7 | 0,82 |
| — Microorganismes, n (%) — | | | |
| Bacilles Gram négatifs (BGN) | **40** | **24** | **0,04** |
| *Enterobacter sp.* | **24** | **8** | **0,01** |
| *Escherichia coli* | 10 | 9 | 0,99 |
| *Pseudomonas aeruginosa* | 0 | 7 | 0,13 |
| *Proteus sp.* | 10 | 2 | 0,08 |
| Autres BGN | 4 | 5 | 0,99 |
| Polymicrobien | 30 | 26 | 0,60 |
| — Traitement antibiotique (définitif) — | | | |
| Bithérapie†d, n (%) | 98 | 91 | 0,11 |
| Fluoroquinolone, n (%) | 48 | 76 | <0,01 |
| Rifampicine, n (%) | 26 | 43 | 0,04 |
| Clindamycine, n (%) | 8 | 50 | 0,01 |
| Durée, jours, médiane (IQR) | 95 (80–106) | 91 (58–109) | 0,25 |

JAC 2024

# Efficacy and safety of co-trimoxazole in device-related bone and joint infections: a CRIOGO multicentre case–control study

Raphaël Lecomte[1,2]*, Colin Deschanvres [1,2], Amandine Le Bourgeois[3], Géraldine Bart[4], Rafaël Mahieu[5], Gwénaël Le Moal[6], Séverine Ansart[7], Nathalie Asseray[1,2], Louise Ruffier d'Epenoux[8], Stéphane Corvec [8,9] and David Boutoille [1,2]; on behalf of the CRIOGO network†

| Variables | Évolution favorable (N=120) | Évolution défavorable (N=30) | Analyse univariée — OR (IC95%) | p | Analyse multivariée — aOR (IC95%) | p |
|---|---|---|---|---|---|---|
| Groupe co-trimoxazole,(%) | 34,2 | 30,0 | 0,81 (0,33–2,01) | 0,65 | 0,8 (0,31–2,06) | 0,64 |
| Sexe féminin, (%) | 37,5 | 43,3 | 1,13 (0,34–3,8) | 0,84 | 0,98 (0,28–3,5) | 0,98 |
| Indice de Charlson, médiane (IQR) | 2 (1–4) | 4 (1,25–5) | 1,37 (0,82–2,31) | 0,23 | 1,25 (0,72–2,15) | 0,43 |
| Ablation du matériel, (%) | 34,2 | 20,0 | 0,43 (0,12–1,48) | 0,18 | 0,5 (0,13–1,93) | 0,31 |

JAC 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Oral versus Intravenous Antibiotics for Bone and Joint Infection

| Caractéristiques | Groupe intraveineux (N=527) | Groupe oral (N=527) | Total (N=1054) |
|---|---|---|---|
| Âge — ans, médiane (IQR) | 61 (49–70) | 60 (49–70) | 60 (49–70) |
| Sexe masculin — n (%) | 320 (60,7) | 358 (67,9) | 678 (64,3) |
| Pseudomonas spp. | **28/500 (5,6)** | **23/503 (4,6)** | **51/1003 (5,1)** |
| Autres bacilles Gram négatifs | **84/500 (16,8)** | **84/503 (16,7)** | **168/1003 (16,7)** |
| Cultures négatives | 77/500 (15,4) | 78/503 (15,5) | 155/1003 (15,5) |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection

| Caractéristiques | Traitement 6 semaines (N=203) | Traitement 12 semaines (N=201) |
|---|---|---|
| Âge — ans, moyenne ± ET | 68,4 ± 11,7 | 69,5 ± 10,7 |
| Sexe masculin — n/total (%) | 143/203 (70,4) | 130/201 (64,7) |
| Monomicrobien — n/total (%) | 166/203 (81,8) | 170/201 (84,6) |
| Multirésistance — n/total (%) | 17/196 (8,7) | 19/192 (9,9) |
| — Pathogènes identifiés — n/total (%) — | | |
| Staphylococcus aureus | 90/237 (38,0) | 70/233 (30,0) |
| Staphylocoques à coagulase négative | 70/237 (29,5) | 82/233 (35,2) |
| Streptococcus spp. | 32/237 (13,5) | 26/233 (11,2) |
| Bacilles Gram négatifs | **21/237 (8,9)** | **26/233 (11,2)** |
| Autres pathogènes | 24/237 (10,1) | 29/233 (12,4) |

**<u>Therapeutic Drug Monitoring :</u>**

Ribera A, et al. Infection 2018

Pfang BG, et al. J Clin Med 2019

Bouige A et al. Med Mal Infect 2019

Gomez-Junyent J et al. Eur J Drug Metab Pharmacokinet 2020

# Osteosynthesis-associated infection of the lower limbs by multidrug-resistant and extensively drug-resistant Gram-negative bacteria: a multicentre cohort study

| Pathogènes (BGN) | MDR % (n=44) | XDR % (n=13) | Total % (n=57) |
|---|---|---|---|
| *Escherichia coli* | 36,36 | — | 28,07 |
| *Pseudomonas aeruginosa* | 15,90 | 53,86 | 24,56 |
| *Enterobacter cloacae* | 18,19 | 7,69 | 15,79 |
| *Klebsiella pneumoniae* | 13,64 | 7,69 | 12,28 |
| *Acinetobacter spp.* | 6,82 | 15,38 | 8,78 |
| *Proteus mirabilis* | 4,55 | 7,69 | 5,26 |
| *Serratia marcescens* | 2,27 | 7,69 | 3,51 |
| *Stenotrophomonas maltophilia* | 2,27 | — | 1,75 |

**Analyse multivariée (modèle de Cox) — facteurs associés à l'évolution**

| Variables | p | HR | IC95 % du HR — Borne inf. | IC95 % du HR — Borne sup. |
|---|---|---|---|---|
| Âge > 60 ans | 0,004 | 3,875 | 1,540 | 9,752 |
| BGN MDR vs XDR* | 0,118 | 0,434 | 0,152 | 1,237 |
| Traitement antimicrobien > 42 j | 0,079 | 2,254 | 0,910 | 5,582 |
| Chirurgies multiples pour IOA | 0,024 | 2,822 | 1,144 | 6,963 |

Giannitsioti et al. JBJI 2025

## Osteosynthesis-associated infection of the lower limbs by multidrug-resistant and extensively drug-resistant Gram-negative bacteria: a multicentre cohort study

- The antimicrobial resistance and duration of treatment did not significantly influence the outcome.
- Independent predictors of the failure to eradicate OAI were age >60 years (hazard ratio, HR, of 3.875; 95 % confidence interval, CI95 %, of 1.540–9.752; p=0.004) and multiple surgeries for OAI (HR of 2.822; CI95 % of 1.144–6.963; p=0.024).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Oral Tebipenem Pivoxil Hydrobromide in Complicated Urinary Tract Infection

**Authors**: Paul B. Eckburg, M.D., Lori Muir, B.Sc., Ian A. Critchley, Ph.D., Susannah Walpole, Ph.D., Hanna Kwak, B.S., Anne-Marie Phelan, M.A., Gary Moore, M.S., Akash Jain, Ph.D., Tim Keutzer, B.A., Aaron Dane, M.Sc., David Melnick, M.D., and Angela K. Talley, M.D. Author Info & Affiliations

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Clinical Trial > NEJM Evid. 2025 Jul;4(7):EVIDoa2400414. doi: 10.1056/EVIDoa2400414. Epub 2025 Jun 24.

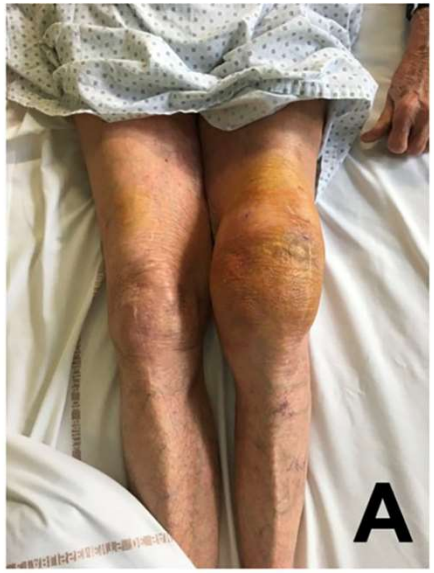
# Sulopenem versus Amoxicillin/Clavulanate for the Treatment of Uncomplicated Urinary Tract Infection

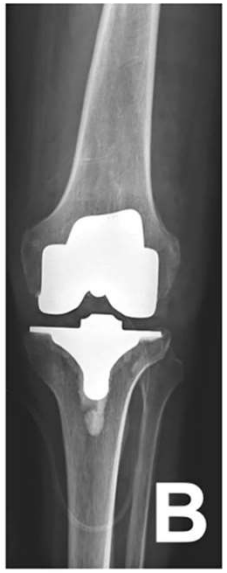
Sailaja Puttagunta [1], Steven I Aronin [2], Jayanti Gupta [3], Anita F Das [4], Kalpana Gupta [5], Michael W Dunne [1]

# PHAGOTHÉRAPIE

# 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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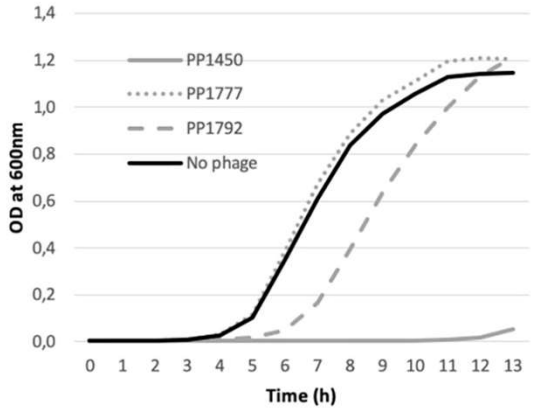
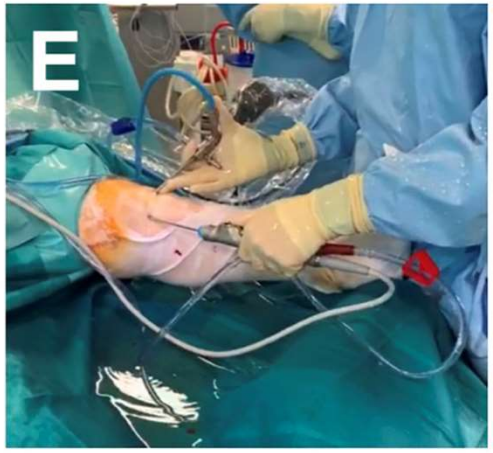
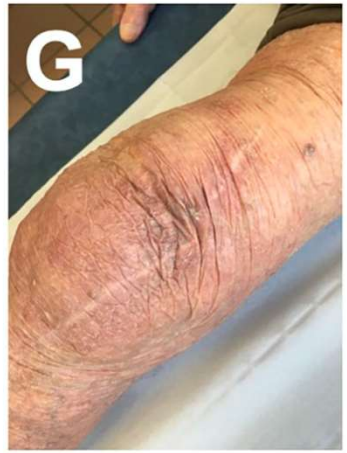



D

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








Frontiers 2021

# Take home message

- Chirurgie ++++
- Tester l'ensemble des options thérapeutiques
- Multidisciplinarité
- Optimiser l'administration
- Doser

- A mon avis : durée non prolongée, relais per os si possible, monothérapie

- FIGURE 1 |
- (A) Left knee joint effusion due to relapsing P.aeruginosaprosthesis knee infection;
- (B) X-ray showing no prosthesis loosening. The susceptibility of the patient's strain to the bacteriophages PP1450, PP1777, and PP1792 (phagogram) was performed using two complementary techniques:
- (C) For the kinetic assay,phages were incubated at a theorical multiplicity of infection (MOI, ratio of phages/bacteria) equal to 100 with the patient's strain. PP1450 was able to inhibit the bacterial growth (gray full line); PP1792 delayed the bacterial growth (gray dotted line) and PP1777 had no impact (gray dashed line).
- (D) For the plaque assay, titers obtained with the patient's strain and the reference strain are determined to calculate the efficiency of plating score (EOP) score (the closer to 1 is the score, the more efficient the phage is). Phages PP1450 and PP1777 were active on the patient's strain with an EOP score of 2.0 10 5 and 4.0 10 6 , respectively. Partial lysis without PFU were observed for PP1792 (considered to have a weak bactericidal or bacteriostatic activity in this assay).
- (E) Arthroscopic DAIR with administration of the phage cocktail at the end of the procedure through the arthroscope.
- (F) Ulceration of a subcutaneous nodule on the external side of the knee observed 2 months after the arthroscopy. (G) Finally, a favorable outcome under suppressive antimicrobial therapy.

# Multidisciplinarité

MERCI