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## Case series of carbapenemase-producing Enterobacteriaceae osteomyelitis: feel it in your bones

B. Davido <sup>a,\*</sup>, L. Noussair <sup>b</sup>, A. Saleh-Mghir <sup>a</sup>, E. Salomon <sup>c</sup>, F. Bouchand <sup>d</sup>, M. Matt <sup>a</sup>, C. Lawrence <sup>b</sup>, T. Bauer <sup>e</sup>, J.L. Herrmann <sup>b,f</sup>, C. Perronne <sup>a</sup>, J.L. Gaillard <sup>c,f</sup>, M. Rottman <sup>b,f</sup>, A. Dinh <sup>a</sup>

<sup>a</sup> *Service des Maladies Infectieuses, Centre Hospitalier Universitaire Raymond Poincaré, AP-HP, Garches, France*

<sup>b</sup> *Laboratoire de Microbiologie, Centre Hospitalier Universitaire Raymond Poincaré, AP-HP, Garches, France*

<sup>c</sup> *Laboratoire de Microbiologie, Centre Hospitalier Universitaire Ambroise Paré, AP-HP, Boulogne-Billancourt, France*

<sup>d</sup> *Pharmacie Hospitalière, Centre Hospitalier Universitaire Raymond Poincaré, AP-HP, Garches, France*

<sup>e</sup> *Service d'Orthopédie, Centre Hospitalier Universitaire Ambroise Paré, AP-HP, Boulogne-Billancourt, France*

<sup>f</sup> *UMR UVSQ INSERM U1173, UFR Simone Veil des Sciences de la Santé, Montigny le Bx, France*

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\* Corresponding author. Fax: +33 1 47 10 77 90.

*E-mail address:* benjamin.davido@aphp.fr (B. Davido).

## ABSTRACT

*Objectives:* Limited data have been reported regarding osteomyelitis due to carbapenemase-producing Enterobacteriaceae (CPE), including co-infections with extended-spectrum  $\beta$ -lactamase (ESBL)-producing micro-organisms.

*Methods:* We conducted a retrospective study in a reference centre for bone and joint infections from 2011–2019 among patients infected with CPE.

*Results:* Nine patients (mean age  $46.8 \pm 16.6$  years), including three with infected implants, were identified. Infections were mostly polymicrobial ( $n = 8/9$ ), including *Staphylococcus aureus* ( $n = 6/9$ ). CPE were mainly OXA-48-type, associated with ESBL-producing Enterobacteriaceae ( $n = 8/9$ ), of which 5/9 isolates were *Klebsiella pneumoniae*. Control of the infection was achieved in seven cases.

*Conclusions:* CPE osteomyelitides are essentially polymicrobial and fluoroquinolone-resistant infections, highlighting the need for efficient surgery with implant removal.

## 1. Introduction

Bone and joint infections (BJIs) are a real concern in the context of the continuous increase in orthopaedic device implantations [1]. *Staphylococcus* spp. and Gram-positive bacteria are the most frequent pathogens responsible for osteomyelitis, whereas Enterobacteriaceae are involved in ~10% of cases [2]. Fluoroquinolones are recommended alone in infections due to Gram-negative bacilli considering their good bone diffusion [3], even in the case of prosthetic joint infection (PJI) [4]. However, resistance to fluoroquinolones has become increasingly prevalent. Indeed, Rodríguez-Pardo et al. reported that in BJIs due to extended-spectrum  $\beta$ -lactamase (ESBL)-producing Enterobacteriaceae (8% of the isolates), 69% were resistant to ciprofloxacin [4].

At the same time, we observe a worldwide increase in carbapenemase-producing Enterobacteriaceae (CPE) [5], especially OXA-48 type in Western Europe [6], meaning that physicians will inevitably be faced with the management of these rare but complex osteomyelitis cases.

To our knowledge, there are only three publications [7–9], beyond a case report [10], addressing this issue, gathering a total of 14 patients. Therefore, new data to evaluate the epidemiology and management of these complex osteomyelitides are necessary, especially since CPE occurs in isolates commonly resistant to other classes of antimicrobial agents, most frequently to the recommended regimen, namely fluoroquinolones.

## 2. Methods

### *2.1. Study setting*

A retrospective study was conducted in a French reference centre for the treatment of BJIs serving the Greater Paris area, organised around weekly pluridisciplinary meetings with an infectious diseases specialist, an orthopaedic surgeon, a microbiologist and a pharmacist. All adult patients admitted for documented osteomyelitis due to CPE from January 2011 to December 2019 were gathered using the laboratory information system (GLIMS v.8; MIPS, Vincennes, France). During this period, our centre managed approximately 2500 BJIs.

### *2.2. Microbiological methods*

At least three intra-operative samples (MED-Extremes) were taken intraoperatively and processed using a bead mill as previously reported [11]. Cultures were performed on solid media with a 5-day incubation under aerobic, anaerobic and CO<sub>2</sub> atmospheres and a 14-day broth enrichment in blood culture media (BACTEC™ Peds Plus™ medium and Lytic Anaerobic medium; BD Diagnostics, Sparks, MD, USA) on a BACTEC™ FX Instrument (BD Diagnostics).

Bacterial identification of all cultured micro-organisms was performed by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Biotyper; Bruker Daltonics, Billerica, MA, USA), and antimicrobial susceptibility testing was performed by the Kirby–Bauer disk diffusion method with diameters digitised using the SIRSCAN system (I2A, Montpellier, France) and

interpreted according to the French implementation [Comité de l'antibiogramme de la Société Française de Microbiologie (CA-SFM)] of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines in use at the time of analysis. Minimum inhibitory concentrations (MICs) of relevant antimicrobial agents were confirmed by Etest (bioMérieux, Marcy-l'Étoile, France; or Liofilchem, I2A) according to EUCAST breakpoints. The mechanism of resistance was determined phenotypically and for CPE was confirmed by carbapenem hydrolysis assays, immunoenzymatic assays or molecular detection assay (Xpert® Carbapenemase Test; Cepheid, Maurens-Scopont, France)

### *2.3. Definitions*

Osteomyelitis was defined both by imaging, including computed tomography (CT) scan and radiography, and a positive bone biopsy, independently of the long bone classification [12].

CPE PJI was defined by the microbiological documentation of an implant infection with two or more intra-operative periprosthetic samples or joint fluid positive for a CPE organism.

Infection control was defined as the absence of local or systemic signs of infection, including delayed wound healing and the absence of relapse needing further procedure. Cases that did not meet the abovementioned criteria were classified as 'failure'.

#### *2.4. Data collection*

The following data were collected: patient characteristics (age, sex, co-morbidities, Charlson comorbidity index, hospitalisation in previous 6 months, stay abroad, hospital length of stay, and rectal and nasal colonisation); infection characteristics [orthopaedic implant (PJI, osteosynthesis, dynamic hip screw fixation), site of infection, micro-organism and mechanism of resistance, and resistance to fluoroquinolones]; treatment characteristics [number of procedures, surgical strategy (i.e. implant retention, removal or debridement), antimicrobial therapy and duration of treatment]; and outcome (evaluated at the last follow-up consultation).

#### *2.5. Statistical analysis*

Descriptive results were expressed using the median and range for continuous variables, where appropriate, and as the number (percentage) for categorical variables. Analyses were performed using Microsoft Excel 2018 (Microsoft Corp., Redmond, WA, USA).

### **3. Results**

#### *3.1. Study population and infection characteristics*

Nine patients with CPE osteomyelitis are presented in Table 1. Of note, all infections occurred in hip joints.



The male:female sex ratio was 8:1, with a mean  $\pm$  standard deviation age of  $46.8 \pm 16.6$  years. The median Charlson comorbidity index was 2 (range 0–10). The median length of stay was 90 days (range 11–240 days).

Interestingly, all patients had previously been hospitalised within the previous 6 months, especially in abroad countries with a high prevalence of CPE ( $n = 8/9$ ).

Infections were mostly polymicrobial ( $n = 8/9$ ), including *Staphylococcus aureus* ( $n = 6/9$ ), with 3/6 being methicillin-resistant *S. aureus* (MRSA).

*Klebsiella pneumoniae* ( $n = 5/9$ ) was the most frequent CPE species identified, followed by *Enterobacter* spp., *Proteus mirabilis*, *Escherichia coli* and *Morganella morganii*. The carbapenemases were most frequently OXA-48-type ( $n = 7/9$ ), followed by NDM-1 ( $n = 3/9$ ). Also, they were widely associated with ESBL-producing Enterobacteriaceae ( $n = 8/9$ ), rarely susceptible to fluoroquinolones ( $n = 2/9$ ) or even co-expressed with ESBLs within the same bacterial host.

### 3.2. Surgical management

The median number of surgical procedures was 3 (range 2–16).

We noted three infected implants, including one osteosynthesis material and two dynamic hip screw fixations. Implants were either removed ( $n = 2$ ) or replaced with a two-step exchange with a gentamicin-loaded spacer prior to re-implantation ( $n = 1$ ).

One patient was disarticulated and three patients benefited from a femoral head and neck resection, reflecting an aggressive strategy.

### *3.3. Antimicrobial prescriptions and outcome*

Antibiotic susceptibility differed widely between patients. The majority of patients were treated with a complex combination therapy using a quadruple therapy ( $n = 3$ ) or triple therapy ( $n = 4$ ). The median duration of treatment was 37 days (range 6–55 days).

Interestingly, two patients had shorter regimens (<7 days) because of a favourable evolution despite the use of an inadequate antimicrobial therapy.

It should be noted that two patients received carbapenems (patient #1 was treated for an OXA-48-type CPE, whilst patient #7 was treated by a synergistic association with fosfomycin for an NDM-1-type CPE). Both infections were considered controlled.

The median follow-up was 10 months (range 3–40 months). Despite disability ( $n = 4/9$ ), we observed a high rate of infection control ( $n = 7/9$ ). Two patients died, including one despite being sterile after persistent bacteraemia with CPE, as previously reported [13].

## 4. Discussion

To the best of our knowledge, this is the largest case series of CPE osteomyelitis published to date. This study retrospectively documented nine cases of osteomyelitis due to CPE. We observed a favourable outcome in the majority of cases, at the expense of complex antimicrobial therapy and a burdened disability (measured in ability to walk, when applicable). This achievement is all the more remarkable given that we experienced a high rate of fluoroquinolone-resistant strains (77.8%; 7/9) like Pfang et al. ( $n = 2/3$ ) [8], but unlike Papadopoulos et al. [9] with <50% resistance or de Sanctis et al. [7] who described 66.7% susceptibility (2/3) to fluoroquinolones.

It is noteworthy that we commonly used last-resort antibiotics, especially intravenous fosfomycin and colistin. As previously reported in our COLITIFOS study [14], both drugs are deemed effective against multidrug-resistant micro-organisms, and fosfomycin benefits from good bone diffusion, with a low rate of acquired-resistance (<3%) [15]. Conversely, when the mentioned last-resort antibiotics are contraindicated or ineffective, new antibiotics such as ceftazidime/avibactam, approved in France in 2016 with a wide marketing authorisation, might be of interest in such a complex situation [16–18].

In the USA in 2014, de Sanctis et al. reported a series of KPC-type carbapenemase-producing *K. pneumoniae* ( $n = 3$ ) complicating PJIs [7]. They observed a high mortality rate ( $n = 2/3$ ) with major disability for the only survivor (disarticulated) and concluded the urgent need for further data and new drugs. In addition, two of their three infections were polymicrobial but without ESBL-producing Enterobacteriaceae,

as in our series. More recently in 2019, Pfang et al. in Spain reported a series of 25 infected orthopaedic implants, including CPE ( $n = 3$ ) [8]. They were exclusively monomicrobial OXA-48-producing *K. pneumoniae*, with a high success rate of infection control ( $n = 2/3$ ). Finally, in 2019 in Greece, Papadoulos et al. reported a large cohort of multidrug-resistant and extensively drug-resistant Gram-negative PJIs, including supposedly CPE ( $n = 8$ ), namely 4 *K. pneumoniae*, 2 *P. mirabilis*, 1 *E. coli* and 1 *Enterobacter cloacae* [9]. The authors showed no influence of colistin administration for extensively drug-resistant bacteria with ~40% infection control. However, these findings might not be appropriated for CPE osteomyelitis because they concerned mainly *Pseudomonas* spp. ( $n = 15$ ).

It is insightful to note that all of the cited studies described patients with orthopaedic implant infections, whereas our series revealed six osteomyelitis cases affecting native joints. This could be explained partly because, historically, Hôpital Raymond-Poincaré is a centre of expertise for road accident victims (particularly spinal cord injuries). These patients are often suffering from complicated pressure sores, responsible for frequent hospitalisations, facilitating in some circumstances (i.e. broad-spectrum antibiotics) infections by multidrug-resistant micro-organisms, including CPE. Since the Arab Spring in 2011, considering its well-established reputation, Hôpital Raymond-Poincaré managed many war-injured patients with complex multidrug-resistant BJIs, explaining the relatively young mean age of our patients.

Finally, our study presents some limitations. First, it is a retrospective study with a relatively limited sample size ( $n = 9$ ) from a centre of reference for the treatment of

BJIs. Therefore, its results might not be extrapolated to other healthcare facilities, especially in other countries, because of OXA-48-type strains. Second, the infections included are heterogeneous, including some orthopaedic implants and native BJIs caused by polymicrobial infections, making it difficult to interpret failures and the value of the different antibiotic strategies used. However, our study emphasises the complexity of CPE osteomyelitis in terms of therapeutics and the need for larger studies conducted by experts to build strong recommendations.

In conclusion, in our case series, CPE osteomyelitides were essentially OXA-48-type, polymicrobial and fluoroquinolone-resistant infections, which makes BJIs so difficult to treat. In the present case, a shorter treatment duration was not associated with failure, highlighting the need for aggressive surgical treatment with implant removal. Further data are needed to evaluate the impact of micro-organisms and their mechanism of resistance on favourable outcome. We believe our work will encourage reference centres to work together to collect enough patients for this particularly rare infection represented by CPE in order to propose the best combination therapy.

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**Competing interests:** None declared.

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments

or comparable ethical standards. Informed consent was not required as the study was a retrospective observational study.

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**Table 1**

Summary of cases with osteomyelitis due to carbapenemase-producing Enterobacteriaceae

Patient #	Year	Sex	Age (years)	Comorbidities	Admission in previous 6 months	Stay abroad	Colonisation	Implant	Localisation	Surgical strategy	No. of procedures	Micro-organisms	FQ	Antimicrobial therapy	Hospital LOS (days)	Outcome	Follow-up (months)
1	2011	M	28	None	Yes	Libya	OXA-48/ESBL <i>Klebsiella pneumoniae</i> , MRSA	No	Hip	Surgical debridement	3	OXA-48/ESBL <i>K. pneumoniae</i> , MRSA, VRE, ESBL <i>Enterobacter cloacae</i>	R	MEM+SXT+AMK+FUS (30 days)	130	Infection controlled with walking mild disability	4

Patient #	Year	Sex	Age (years)	Comorbidities	Admission in previous 6 months	Stay abroad	Colonisation	Implant	Localisation	Surgical strategy	No. of procedures	Micro-organisms	FQ	Antimicrobial therapy	Hospital LOS (days)	Outcome	Follow-up (months)
2	2013	M	36	None	Yes	Libya	OXA-48/ESBL <i>K. pneumoniae</i>	No	Hip	Disarticulation	5	OXA-48/ESBL <i>K. pneumoniae</i> , ESBL <i>Proteus mirabilis</i> , ESBL <i>Escherichia coli</i> , <i>Enterococcus faecalis</i> , <i>Corynebacterium striatum</i>	R	TZP+COL+RIF+ FOS (10 days) and finally TZP+COL+TG C (45 days)	240	Alive with major disability	12

Patient #	Year	Sex	Age (years)	Comorbidities	Admission in previous 6 months	Stay abroad	Colonisation	Implant	Localisation	Surgical strategy	No. of procedures	Micro-organisms	FQ	Antimicrobial therapy	Hospital LOS (days)	Outcome	Follow-up (months)
3	2015	M	29	Paraplegia	Yes	Morocco	OXA-48/ESBL <i>Enterobacter aerogenes</i> , OXA-48 <i>Citrobacter koseri</i> , OXA-48 <i>E. coli</i>	No	Hip	Femoral head and neck excision	10	OXA-48/ESBL <i>E. aerogene</i> s, MSSA, <i>C. amycolatum</i>	I	TZP (3 days) and finally LVX (3 days)	35	Infection control	36

Patient #	Year	Sex	Age (years)	Comorbidities	Admission in previous 6 months	Stay abroad	Colonisation	Implant	Localisation	Surgical strategy	No. of procedures	Micro-organisms	FQ	Antimicrobial therapy	Hospital LOS (days)	Outcome	Follow-up (months)
4	2016	F	72	Cirrhosis, stroke	Yes	Algeria	OXA-48/ESBL <i>K. pneumoniae</i>	DHS fixation	Hip	Implant removal	2	OXA-48/ESBL <i>K. pneumoniae</i> , OXA-48 <i>K. pneumoniae</i>	R	TZP (7 days)	11	Infection control	40
5	2016	M	69	Diabetes	Yes	Algeria	OXA-48 <i>E. cloacae</i>	Osteosynthesis	Hip	Implant removal	4	OXA-48 <i>E. cloacae</i> , NDM-1 <i>E. cloacae</i> , <i>E. faecalis</i> , MSSA	S	COL+LVX+AMX (30 days) and finally ATM+CAZ/AVI (14 days)	130	Died	3.6
6	2016	M	49	Diabetes, multiple sclerosis	Yes	No	Negative	No	Hip	Femoral head and neck excision	2	OXA-48/ESBL <i>E. coli</i> , <i>P. mirabilis</i>	S	FOS+CIP (45 days)	21	Infection control	24

Patient #	Year	Sex	Age (years)	Comorbidities	Admission in previous 6 months	Stay abroad	Colonisation	Implant	Localisation	Surgical strategy	No. of procedures	Micro-organisms	FQ	Antimicrobial therapy	Hospital LOS (days)	Outcome	Follow-up (months)
7	2016	M	36	None	Yes	Egypt	MRSA	No	Hip	Surgical debridement	2	NDM-1/ESBL <i>E. cloacae</i> , <i>E. faecalis</i> , <i>C. sporogenes</i>	I	AMK (7 days)+MEM+FOS+DAP (45 days)	18	Infection controlled with severe walking disability	7
8	2018	M	59	Paraplegia	Yes	Thailand	OXA-48/ESBL <i>K. pneumoniae</i>	No	Hip	Femoral head and neck excision	3	OXA-48 <i>K. pneumoniae</i> , OXA-48 <i>Morganella morganii</i> , MSSA	R	FOS+COL+TGC (35 days)	90	Died	3

Patient #	Year	Sex	Age (years)	Comorbidities	Admission in previous 6 months	Stay abroad	Colonisation	Implant	Localisation	Surgical strategy	No. of procedures	Micro-organisms	FQ	Antimicrobial therapy	Hospital LOS (days)	Outcome	Follow-up (months)
9	2018	M	43	None	Yes	Algeria and Tunisia	Negative	DHS	Hip	Spacer + gamma nail and finally prosthetic joint	16	NDM-1/ESBL <i>K. pneumoniae</i> , MRSA, <i>P. mirabilis</i>	R	CAZ/AVI+ATM+ DAP (37 days)	95	Infection controlled with minor walking disability	8

FQ, fluoroquinolone; LOS, length of stay; ESBL, extended-spectrum  $\beta$ -lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; R, resistant; MSSA, methicillin-susceptible *Staphylococcus aureus*; I, intermediate; DHS, dynamic hip screw; S, susceptible; MEM, meropenem; SXT, trimethoprim/sulfamethoxazole; AMK, amikacin; FUS, fusidic acid; TZP, piperacillin/tazobactam; COL, colistin; RIF, rifampicin; FOS, fosfomicin; TGC, tigecycline; LVX, levofloxacin; AMX, amoxicillin; ATM, aztreonam; CAZ/AVI, ceftazidime/avibactam; CIP, ciprofloxacin; DAP, daptomycin.