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## Clostridial prosthetic joint infections: a series of 16 cases and literature review

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### Competing interests

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### Highlights:

- *C. perfringens* was the most frequently involved species in this series of clostridial PJIs
- Patients experiencing clostridial PJI were elderly at the time of arthroplasty and PJI
- Most of the PJIs in this series were early- or delayed-onset infections
- The prognosis for clostridial PJIs remains poor
- DAIR with a 12-week antimicrobial therapy may be a suitable strategy

### Abstract:

Objectives: Prosthetic joint infections (PJIs) due to the *Clostridium* species have not been widely investigated. We aimed to characterize these uncommon infections. Methods: We conducted a retrospective study between 2003 and 2020 in six French hospitals combined with a review of the literature. Results: The main conclusions obtained from the 16 patients included were reinforced by the literature analysis: (i) *Clostridium perfringens* was the most frequently involved species, (ii) patients presented an advanced age at the time of prosthesis placement and infection, (iii) most of the infections were early- or delayed-onset, (iv) the prognosis for these PJIs remains poor, (v) when performed (n=5), DAIR with 12-week antimicrobial therapy led to a favorable outcome in 80% of cases. Conclusions: Given the low incidence of this infection, our work represents the largest series of clostridial PJIs reported to date and highlights some specificities of these infections. Further prospective studies are needed to confirm these results.

**List of abbreviations**

BMI: Body Mass Index

CKD: Chronic Kidney Disease

DAIR: Debridement, Antibiotics with Implant Retention

IQR: InterQuartile Range

MD: Missing Data

NA: Not Applicable

PJI: Prosthetic Joint Infection

THA: Total Hip Arthroplasty

TKA: Total Knee Arthroplasty

## 1. Introduction

Prosthetic joint infections (PJIs) are one of the major complications occurring after prosthetic joint implantation, leading to significant morbidity [1,2]. They are usually classified into three schemes depending on the time of onset after surgery [1,2]. Early- and delayed-onset PJIs (occurring within the first three months or between three and 24 months after the last surgery, respectively) are commonly recognized as being acquired at the time of surgery, whereas late infections (occurring more than 24 months after surgery) are considered as being caused by hematogenous seeding from infection at another site [2]. Most cases require revision surgery followed by prolonged antibiotic treatment. Medical and surgical strategies depend largely on time of onset after surgery [2]. Whereas *Cutibacterium acnes* is frequently involved in shoulder PJIs, other anaerobic bacteria remain unusual causative agents of PJIs, frequently appearing in polymicrobial infections [2,3].

*Clostridium* species are Gram-positive, spore-forming, anaerobic rods, ubiquitous in the environment and components of digestive flora [4]. Responsible for a broad array of infections, including invasive and toxin-mediated processes [4], *Clostridium* species have been implicated in native joint septic arthritis but only exceptionally reported in PJIs [3,5]. Given their low incidence, clostridial PJIs have been only loosely described. The present work is aimed at better characterizing these infections, through a retrospective multicenter study and a review of the literature.

## 2. Material and methods

All patients diagnosed with a PJI involving at least one clostridial species, between 2003 and 2020, were retrospectively identified in six hospitals of Western France. Polymicrobial infections were not excluded. PJI diagnosis was defined according to IDSA guidelines [1]. Medical charts were retrospectively reviewed in order to collect clinical and microbiological data.

*Clostridium perfringens* strains available at the time of the study were sent to the National Reference Center for Anaerobic bacteria and Botulism, (Pasteur Institute, Paris, France) to define their toxinotype. Specific PCR tests were performed to detect the structural genes encoding the most common toxins produced by *C. perfringens* ( $\alpha$ -toxin,  $\beta$ -toxin,  $\delta$ -toxin,  $\epsilon$ -toxin,  $\iota$ -toxin, *Clostridium perfringens* enterotoxin (CPE),  $\theta$ -toxin, NetB, TpeL, and BEC). Strains were then classified according to the toxin-based typing scheme proposed by Rood et al [6].

A literature review was conducted and all cases of *C. perfringens* PJIs reported before 2021 in PubMed database were identified. Articles with major missing clinical data or that were not English- language were excluded.

## 3. Results

### 3.1 Case description

Sixteen patients met the inclusion criteria during the study period (**Table 1**). Median (interquartile range [IQR]) ages at the time of prosthesis placement and at the time of infection were 77 years (71;84) and 84.5 years (79.5;86) respectively. No patient showed any evidence of gas gangrene or identified skin portal of entry. A digestive portal of entry was identified in four patients (25%). When performed (n=14), concomitant blood cultures were negative in 93% of the cases (n=13). Fourteen (87.5%) PJIs were early- or delayed-onset infections (see **Figure 1** for more details on time to onset).

*C. perfringens* was the most frequently involved species (15/16, 93.7%), and as part of polymicrobial infections in 7/15. In most cases (n=12), all samples were positive for clostridial species. In other cases, four out of five (n=1), three out of five (n=1), two out of five (n=1) and one out of three (n=1) samples were culture-positive. Molecular analysis (performed on 10 strains) identified strains producing  $\alpha$ -toxin

alone (n=1),  $\alpha$ - and  $\theta$ -toxins (n=4),  $\alpha$ -,  $\theta$ - and  $\beta$ -toxins (n=4), and  $\alpha$ -,  $\theta$ -,  $\beta$ -toxins and enterotoxin (CPE) (n=1). Therefore, they all belonged to toxinotypes A (n=5) or C (n=5).

DAIR (debridement, antibiotics with implant retention) procedure was the most frequently performed surgical intervention (n=7). Three other patients were treated surgically by a one-stage exchange, four a two-stage exchange, one underwent resection without replacement, and one did not undergo surgery. Despite variability among the antimicrobial agents used, amoxicillin was the most prescribed drug (n=8), alone (n=2) or in association (n=6). Clindamycin was also frequently used (n=6), always in association with other molecules (amoxicillin (n=3), metronidazole (n=1), rifampicin (n=1), or levofloxacin (n=1)). Metronidazole was prescribed in four patients, alone (n=1) or in association (clindamycin (n=1), amoxicillin (n=1), levofloxacin + rifampicin (n=1)). Median treatment duration was 11.5 weeks (6.75;12).

When available (n=11), outcomes within the 24 following months were favorable (n=5) or complicated by relapse (n=1), chronic fistula (n=1), or PJI-related death (n=4). Outcomes depending on surgical strategies and antimicrobial treatment duration are presented in *Supplementary Table 1*. When performed (n=5), DAIR combined with a 12-week antimicrobial treatment was associated with a high success rate (80%).

### 3.2 Literature review

The literature review focused on PJIs due to *C. perfringens* since it was the species most frequently implicated in the reported cases. Seven articles were eligible, yielding a total of nine cases of *C. perfringens* PJIs [7–13]. Their main clinical features are summarized in *Table 2* and compared with our clinical series in *Table 1*. Median age (IQR) at the time of the infection was 71 years (64-80). The majority of PJIs were early- or delayed-onset infections (n=8). Only one patient (11%) had a concomitant positive blood culture, while another had an underlying gastrointestinal disease (cholecystitis). Surgical management was heterogeneous. The most frequently used antibiotics were penicillin (n=6) and clindamycin (n=5), generally as components of combination antimicrobial therapies. Antibiotic treatment duration was mainly limited to six weeks. According to the authors, no relapse occurred during the post-infection follow-up period.

## 4. Discussion

Due to the low incidence of clostridial PJIs, data on these infections are scarce. Therefore, we carried out a retrospective multicenter study combined with a review of the literature to more specifically characterize the PJIs due to *Clostridium* sp. Interestingly, the main conclusions obtained from the case series were reinforced by the literature analysis.

Regarding risk factors, this work suggests special features related to clostridial PJIs. In this study patients suffering from clostridial PJIs were relatively elderly at the time of prosthesis placement and the time of infection, whereas the previous literature identified younger age (<60 years) as a risk factor for PJI [14,15].

As the *Clostridium* species belong to the digestive flora [4], hematogenous seeding from a digestive portal of entry could be assumed as the main mechanism by which clostridial PJIs are initiated. That said, an underlying gastrointestinal disease was identified in only 4/16 and 1/9 patients included in our series and in the literature review, respectively. Moreover, blood cultures were unusually positive (1/14 and 1/9 in our series and in the literature, respectively, and both cases were late-onset PJIs). Of note, the majority of clostridial PJIs were early-onset infections, commonly recognized as being acquired at the time of surgery [2]. Taken together, these characteristics could suggest (i) direct contamination of the surgical site during prosthesis implantation, or (ii) contiguous spread of an early

post-operative superficial surgical site infection. The hip, which is the closest joint to the orifice of the digestive tract, was also the most affected joint. Furthermore, polymicrobial infections, often associating other commensals from the gastrointestinal tract, were frequent.

Another major finding of this work is that *C. perfringens* was by far the most frequently isolated species. The ability to produce toxins is essential to the virulence of *C. perfringens* and some toxins are involved in specific diseases [6]. Analysis of toxin production analysis did not highlight a specific toxin associated with PJIs. In fact, the analyzed strains were able to produce various combinations of four different toxins and belonged to toxinotypes A (n=5) or C (n=5), which are also the most represented toxinotypes.

Regarding the management of clostridial PJIs, our work underlines considerable heterogeneity, in both antimicrobial treatment and surgical strategies. Many reasons could explain these disparities. First, except for *C. acnes*, no specific recommendations have been published regarding antimicrobial management of anaerobic PJIs [1]. Secondly, almost half of the included patients presented a polymicrobial infection. Associated pathogens might have affected antimicrobial choices. Thirdly, cases were collected over 18 years and in six different centers, which might have appended some additional variations. However, some outlines can be drawn. Penicillin, clindamycin, and metronidazole were the most widely prescribed drugs, mainly in combination with other antibiotics. It bears mentioning that *C. perfringens* is particularly susceptible to these three molecules [16,17], as has been suggested for clostridial PJIs [3]. Median duration of antimicrobial treatment was 12 weeks, as recommended when the prosthesis is retained [1]. From a surgical standpoint, almost half of the patients had undergone a DAIR procedure. The high proportion may be explained by the large number of early-onset infections, for which DAIR is recommended [2].

Regarding outcomes, clostridial PJIs were associated in our series with a poor prognosis, as death or relapse accounted for half of the cases. In the review of the literature, no relapse was reported but follow-up duration was always inferior to 24 months. Interestingly, the combination of DAIR procedure and a 12-weeks antimicrobial therapy was associated with a high success rate (80%). However, considering the low number of included patients and the volume of missing data, no conclusion could be drawn concerning the most successful strategy.

The main limitations of this study include its retrospective and descriptive design, and the small size of the analyzed population.

## 5. Conclusions

Given the low incidence of this infection, our work nevertheless represents the largest series of clostridial PJIs reported to date and highlights some specificities of these uncommon infections: (i) *C. perfringens* was the most frequently involved *Clostridium* species, (ii) patients presented an advanced age at the time of prosthesis placement and infection, (iii) most of the infections were early- or delayed-onset infections, (iv) these PJIs are associated with a poor prognosis (death or relapse), (v) when performed (n=5), DAIR procedure with prolonged antibiotic treatment led to favorable outcome in 80% of cases.

## Ethical statement

According to the French and European legislations, the use of anonymous data does not require the approval of the ethics committee. This study was registered in the Nantes Hospital by the local Data Protection Officer under reference TS005-BIO-AP-2019\_12.

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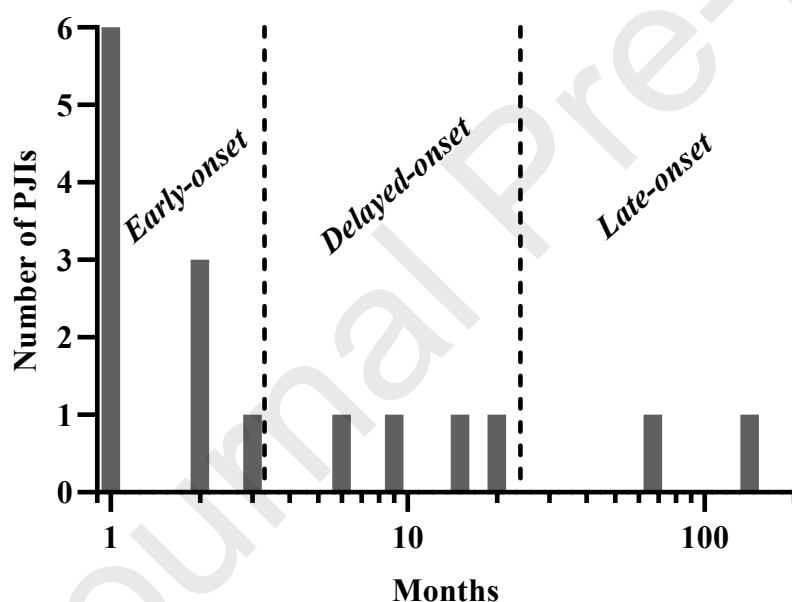
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**Figure 1. Time to onset of PJIs**



**Table 1.** Main characteristics of the 16 patients with *Clostridium* sp. prosthetic joint infections included in our series, compared with data from the literature.

	Our series (n=16)	Literature review (n=9)
<b>Study population</b>		
Male gender, n (%)	4 (25)	5(55.5)

Age at the time of prosthesis placement, years, median (IQR)	77 (71;84) <sup>a</sup>	-
	84.5	70 (63;81)
Age at the time of infection, years, median (IQR)	(79.5;86)	-
BMI, kg/m <sup>2</sup> , median (IQR)	26 (23;29) <sup>b</sup>	-
- BMI ≥ 35 (kg/m <sup>2</sup> ), n (%)	3 (18.8)	-
Tobacco use <sup>c</sup> , n (%)	0 (0)	-
Diabetes <sup>d</sup> , n (%)	3 (21.4) <sup>e</sup>	-
Immunosuppression <sup>f</sup> , n (%)	6 (42.9) <sup>g</sup>	-
CKD <sup>h</sup>	5 (35.7) <sup>i</sup>	-
Primary orthopaedic disease, n (%) <sup>j</sup>		-
- Osteoarthritis	6 (46.1)	-
- Fracture		-
- Osteonecrosis	5 (38.5)	-
- Aseptic loosening	1 (7.7)	-
Previous surgery on index joint, n (%) <sup>k</sup>	1 (7.7)	-
	8 (53.3)	-
<b>Type of prosthesis</b>		
THA, n (%)	11 (68.75)	7 (77.8)
Hip hemiarthroplasty, n (%)	1 (6.25)	0 (0)
TKA, n (%)	4 (25)	2 (22.2)
<b>Type of infection</b>		
Early (<3 months after the last surgery), n (%)	10 (62.5)	7 (77.8)
Delayed (3 months to 24 months after the last surgery), n (%)	4 (25)	1 (11.1)
	2 (12.5)	1 (11.1)
Late (>24 months after the last surgery), n (%)		
<b>Microorganisms</b>		
Monomicrobial infection, n (%)	9 (56.2)	7 (77.8)
Polymicrobial infection, n (%)	7 (43.8) <sup>l</sup>	2 (22.2) <sup>m</sup>
<i>Clostridium perfringens</i> , n (%)	15 (93.7)	9 (100)

- Toxinotype A, n (%) <sup>n</sup>	5 (50)	-
- Toxinotype C, n (%) <sup>n</sup>	5 (50)	-
<i>Clostridium clostridioforme</i> , n (%)	1 (6.3)	-
<i>Clostridium sordelii</i> , n (%)	1 (6.3)	-

### Treatment management

#### Surgery

DAIR, n (%)	7 (43.75)	2 (22.2)
One-stage exchange, n (%)	3 (18.75)	0 (0)
Two-stage exchange, n (%)	4 (25)	3 (33.3)
Arthroplasty resection without reimplantation, n (%)	1 (6.25)	2 (22.2)
No surgery, n (%)	1 (6.25)	2 (22.2)

#### Antibiotic therapy

Penicillin or amoxicillin +/- clavulanic acid, n (%)	8 (50)	6 (66.6)
- Alone, n (%)	2 (25)	1 (16.7)
- Co-administrated antibiotic, n (%)	6 (75) <sup>o</sup>	5 (83.3) <sup>p</sup>
Other, n (%)	8 (50)	3 (33;3)
Duration, weeks, median (IQR) <sup>q</sup>	11.5 (6.75;12)	6 (6;12)

### Outcome (within the 24 following months)<sup>r</sup>

Favorable, n (%)	5 (45.5)	
Relapse, n (%)	1 (9)	MD: follow-up < 24 months
Chronic fistula, n (%)	1 (9)	
Death related to PJI, n (%)	4 (36.5)	

**Abbreviations:** n, number; IQR, interquartile range; BMI, body mass index; CKD, chronic kidney disease; THA, total hip arthroplasty; TKA, total knee arthroplasty; DAIR, debridement, antibiotics with implant retention; MD, missing data; PJI, prosthetic joint infection.

<sup>a</sup> missing data: n=1, <sup>b</sup> missing data: n=1, <sup>c</sup> current smoking, <sup>d</sup> patients treated with insulin or oral medications, <sup>e</sup> missing data: n=2, <sup>f</sup> including drugs (corticosteroids and chemotherapy) and cancer (active disease or treated for less than one year), <sup>g</sup> missing data: n=2, <sup>h</sup> Glomerular filtration output <60 mL/min (Gault and Cockcroft formula), <sup>i</sup> missing data: n=2, <sup>j</sup> missing data: n=3, <sup>k</sup> missing data: n=1, <sup>l</sup> associated bacteria: methicillin-susceptible *Staphylococcus aureus* (n=4) *Fingoldia magna* (n=2) methicillin-resistant *Staphylococcus epidermidis* (n=1) *Enterococcus faecalis* (n=1) *Anaerococcus prevotii* (n=1), <sup>m</sup> associated bacteria: *Pseudomonas pyocyanea* (n=1) *Proteus vulgaris* (n=1) *F. magna* (n=1) *Peptoniphilus harei* (n=1), <sup>n</sup> missing data n=5,

<sup>o</sup> co-administrated molecules: clindamycin (n=3), rifampicin (n=1), metronidazole (n=1), vancomycin (n=1), <sup>p</sup> co-administrated molecules: cloxacillin (n=2), fusidic acid (n=1), clindamycin (n=2), <sup>q</sup> missing data: n=4, <sup>r</sup> loss to follow-up (n=5).

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**Table 2.** Literature review of PJIs due to *C. perfringens*

Reference	Age, Sex	Type of prosthesis	Delay sepsis	Type of infection	Microbiology	Surgical management	Antimicrobial therapy	Antimicrobial therapy duration	Follow-up duration	Relapse according to the authors
Rush et al, 1976	62, M	THA	< 24h	Early	<i>C. perfringens</i> , <i>P. pyocyanea</i>	DAIR followed by chronic fistula	Penicillin and cloxacillin	MD	MD	NA
Rush et al, 1976	66, F	THA	< 24h	Early	<i>C. perfringens</i>	No surgery	Penicillin and cloxacillin	MD	MD	No
Kibbler et al, 1991	77, F	THA	5 years	Late	<i>C. perfringens</i>	No surgery	Penicillin and fusidic acid	6 weeks	19 months	No
Vogely et al, 1999	52, F	THA	16 months	Delayed	<i>C. perfringens</i>	Two-stage exchange	Penicillin and clindamycin	MD	18 months	No
Pearle et al, 2003	82, M	TKA	3 weeks	Early	<i>C. perfringens</i>	Two-stage exchange	Penicillin	6 weeks	20 months	No
Lazzarini et al, 2004	80, F	THA	1 week	Early	<i>C. perfringens</i>	DAIR	Penicillin and clindamycin	6 weeks	12 months	No
Stroud G et al, 2020	64, M	TKA	4 weeks	Early	<i>C. perfringens</i>	Two-stage exchange	Clindamycin and metronidazole	6 weeks	12 months	No

Visse et al, 2021	70, M	THA	MD	Early	<i>C. perfringens</i>	Implant removal	Clindamycin and rifampicin then metronidazole	12 weeks (8 + 4)	3 months	MD <sup>a</sup>
Visse et al, 2021	86, M	THA	MD	Early	<i>C. perfringens</i> , <i>P. vulgaris</i> , <i>F. magna</i> , <i>P. harei</i>	Implant removal	Cotrimoxazole, levofloxacin and metronidazole then clindamycin	12 weeks (4 + 8)	4 months	MD <sup>a</sup>

**Abbreviations:** MD, missing data; NA, not applicable; THA, total hip arthroplasty; TKA, total knee arthroplasty; DAIR, debridement, antibiotics with implant retention; PJI, prosthetic joint infection.

<sup>a</sup> death not related to PJI during the follow-up period